American Heart Journal

An international publication for the study of the circulation

GEORGE E. BURCH M.D
Editor

HARRY L. COLCOLOUGH M.D
NICHOLAS P. DePASQUALE, M.D
JOHN H. PHILLIPS M.D
Assistant editors

1430 Tulane Avenue, New Orleans La. 70112
The C. V. Mosby Company 3207 Washington Blvd. St. Louis Mo. 63103

VOLUME 77

JANUARY-JUNE, 1969

VOLUME 77

Printed in the United States of America

American Heart Journal

JANUARY 1969

Contents

continued on page 8

Contents *continued*

continued on page 7

Vol. 77 No. 1, January 1969 American Heart *Journal* is published monthly by The C. V Mosby Company 3207 Washington Blvd., St. Louis, Mo. 63103 *Annual subscription rates*—United States and its possessions institutional (multiple-reader) subscriptions, $21.00; personal (regular) subscriptions† $17.50, student, intern, and resident physician subscriptions† $10.50 Canada and Mexico institutional (multiple-reader) subscriptions, $22.50; personal (regular) subscriptions, $20.00 student, intern and resident physician subscriptions, $11.00 Other countries institutional (multiple-reader) subscriptions, $2[illegible].50 personal (regular) subscriptions, $21.00; student, intern, and resident physician subscriptions, $14.00. Single copies, $1.50 postpaid

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics city county state, province, and national government bureaus and departments and all commercial and private institutions and organizations

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

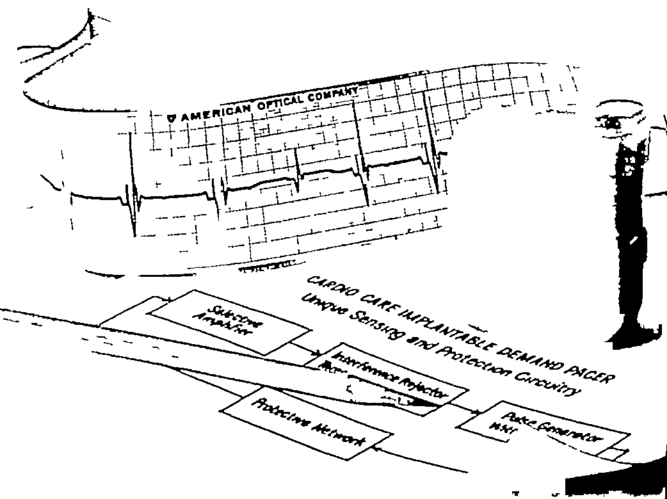
Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Book reviews



AMERICAN OPTICAL COMPANY
CARDIO CARE IMPLANTABLE DEMAND PACER
Unique Sensing and Protection Circuitry
Selective Amplifier
Interference Rejector
Protective Network
Pulse Generator

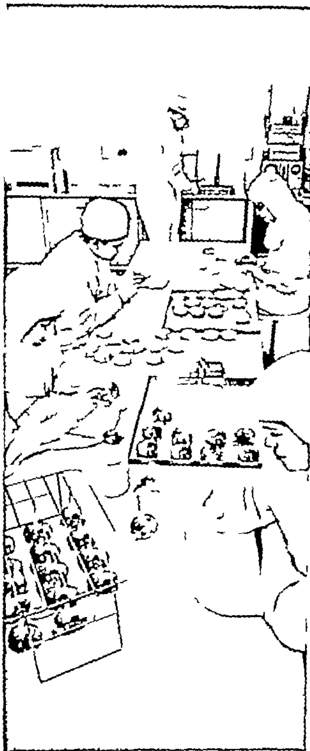
American Heart Journal

FEBRUARY 1969

Contents

Editorial

continued on page 5



Contents *continued*

Experimental and laboratory reports

Case reports

continued on page 7

Vol. 77, No. 2, February, 1969. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. *Annual subscription rates*—United States and its possessions: Institutional (multiple-reader) subscriptions,* $21.00; personal (regular) subscriptions,† $17.50; student, intern, and resident physician subscriptions,† $10.00. Canada and Mexico: Institutional (multiple-reader) subscriptions,* $21.50; personal (regular) subscriptions, $20.00; student, intern, and resident physician subscriptions, $13.00. Other countries: Institutional (multiple-reader) subscriptions, $24.50; personal (regular) subscriptions, $21.00; student, intern, and resident physician subscriptions, $14.00. Single copies, $3.50 postpaid.

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and clinics; city, county, state, province, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

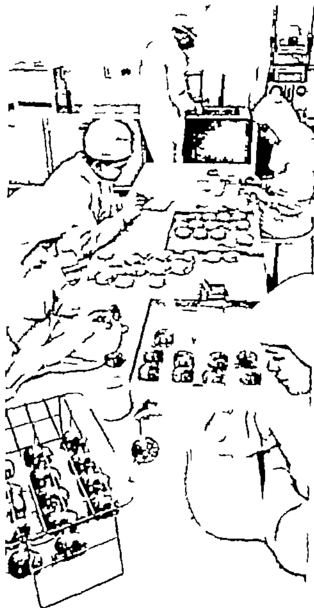
Contents *continued*

American Heart Journal

MARCH 1969

Contents

continued on page 5





Case reports

Review

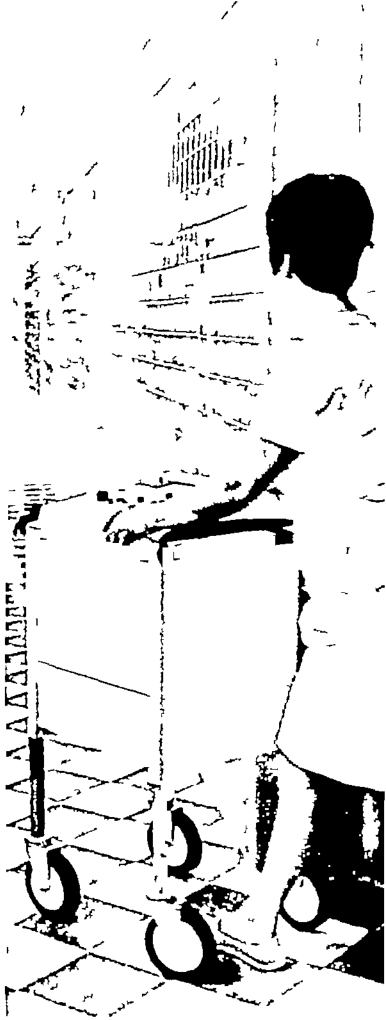
continued on page

Vol. 77 No 3 March, 1969 American Heart Journal is published monthly by The C. V Mosby Company 3207 Washington Blvd., St Louis, Mo 63103. Annual subscription rates—United States and its possessions institutional (multiple-reader) subscriptions, $2 00; personal (regular) subscriptions, $17.50, student, intern, and resident physician subscriptions, $10.50 Canada and Mexico institutional (multiple-reader) subscriptions. $22.50 personal (regular) subscriptions, $20 00, student, intern, and resident physician subscriptions, $13 00. Other countries institutional (multiple-reader) subscriptions, $24.50, personal (regular) subscriptions, $21.00 student, intern, and resident physician subscriptions, $14 00. Single copies, $3.50 postpaid.

Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and citizen city county state, province, and national government bureaus and departments and all commercial and private institutions and organizations.

Personal (regular) subscriptions, and all student-rate subscriptions must be in the name of, and billed to, individuals. Second class postage paid at St. Louis, Mo.

Contents *continued*

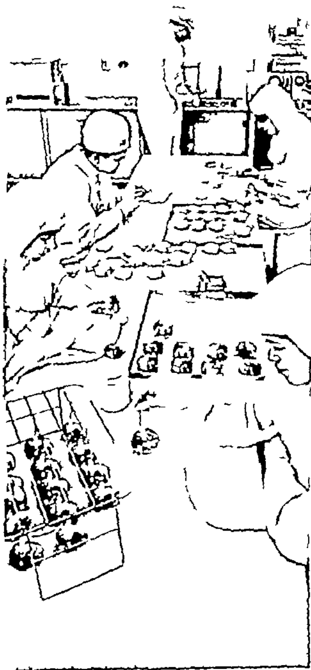


American Heart Journal

APRIL 1969

Contents

continued on page 5



MEDTRONIC "Operates" in an Immaculate Field Every Step of the Way

Throughout the entire manufacture of a Medtronic pacemaker clean conditions are p eserved The electron c components that comprise the pacemaker pulse generator are assembled under particle-free conditions. Then the pacemaker is taken to a clean room into which traffic is severely restricted. Technicians *do a ste ile scrub don special clothes and* sterile surgical gloves and take an air shower in an anteroom before entering the clean room. In the clean room final coating of pacemakers and electrodes is done under immaculate conditions the entire assembly is qual ty checked given an alcohol wash, and sealed into a plastic f lm pouch The final package is then gas sterilized. A spore strip inserted with each sterilizer load is checked to verify steril ty of the units. Units are quarantined until spore strip is read. The ultimate result is that when the surgeon is in the operating room e dy fo mplantat on he knows that the Medtronic pacemaker he is about to install is sterile and free of foreign bodies.

P pe st ri zat on s only one of many Medtronic standards. Others are complete serial numbering, clearly stated pacemaker rate I body temperature, the use of X-rays to verify quality and establish package integrity and docume t ng of f nal test ng date A card packed with each pacemaker lists the output parameters of that unit as tested. Each unit returned to Medtronic that has been taken out of a patient for elective replacement is studied and checked. Its characteristic data are compared to the data on the original Quality Control card for analysis.



Medtronic, Inc.

3055 HIGHWAY EIGHT MINNEAPOLIS MINNESOTA 55418

AREA 612/781 6055

continued on page 7

Vol. 77, No. 4, April 1969. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. Annual subscription rates—United States and its possessions: institutional (multiple-reader) subscriptions, $[illegible]; personal (regular) subscriptions, $17.50; student, intern, and resident physician subscriptions, $[illegible]. Canada and Mexico: institutional (multiple-reader) subscriptions, $23.50; personal (regular) subscriptions, $20.00; student, intern, and resident physician subscriptions, $13.00. Other countries: institutional (multiple-reader) subscriptions, $24.50; personal (regular) subscriptions, $21.00; student, intern, and resident physician subscriptions, $1[illegible].00. Single copies, $1.80 postpaid.

Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and offices of city, county, state, province, and national government bureaus and departments, and all commercial and private institutions and organizations.

Personal (regular) subscriptions and all student-rate subscriptions must be in the names of, and billed to, individuals.
Second class postage paid at St. Louis, Mo.

Contents *continued*

Fundamentals of clinical cardiology

Appraisal and reappraisal of cardiac therapy

Annotations

Book reviews

Announcements

angina minutes away

Sorbitrate Sublingual

ISOSORBIDE DINITRATE 5mg.

acts in 2 to 5 minutes / lasts 1 to 2 hours

Also available: Sorbitrate (isosorbide dinitrate) Oral 5 and 10 mg. Sorbitrate 10 mg. with Phenobarbital 15 mg.

Mode of action: The mechanism of action of Sorbitrate (isosorbide dinitrate) in the relief of angina pectoris is unknown at this time although the basic pharmacologic action is to relax smooth muscle. Isosorbide dinitrate reduces in number and severity the incidence of angina pectoris attacks, with concomitant reduction in nitroglycerin intake. **Indications:** *Sublingual:* For the prevention and treatment of angina pectoris. *Oral:* For the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode. Sorbitrate with Phenobarbital is indicated for patients in whom the angina pectoris is accompanied by anxiety or its related symptoms. **Contraindications:** A history of sensitivity to the drug. **Warnings:** Data supporting the use of nitrates during the early d ys of the acut phase of myocardial infarction (the period during which clinical and labor tory findings av able) in fficient to es blish s fety. Phenob b al may be h bit f rming. **Precautions:** Should be sed with caution in patients ho have glaucoma. Tol er nce t thi drug, and cros tolerance othe nitrit and nitrates may occu . *Adverse Reactions:* *Headache* is the most common and may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which ually diminish or disappear as therapy is continued. *Adverse reactions* seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and eakness as ell as other signs of cerebral ischemi associated ith postural hypotension. Individual marked sensitivity to the hypotensive effects of nitrates. Certain severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis. This drug can act as physiological antagonist to norepinephrine, acetylcholine, histamine and other agents. **Dosage and Administration:** *Route:* Sublingual and oral tablets. *Ind id al Dos* 5 to 10 mg. by either route of administration is the range commonly used although individual dosages of up to 30 mg. have frequently been employed. *Dosage Schedule:* Smallest effective dose p n necessary for the prevention and treatment of anginal attack at 4 to 6 hour intervals sublingually or 3 to 4 times daily orally. Although the onset of effect and the duration of effect of this drug are quite variable the following are the generally reported ranges of these alues. *Onset f Effect: S blingual:* 2 to 5 minutes. *Oral:* 15 to 30 minutes. *Duration of Effect: Sublingual:* 1 to 2 hours. *Oral:* Estimated to be 4 to 6 hours.

For full prescribing information, see pack ge insert

Stuart Division ICI US CHEMICAL INDUSTRIES INC. / Pasadena Ca. 91109

American Heart Journal

MAY 1969

Contents

continued on page 5

Contents *continued*

continued on page 7

Vol. 77, No. 5, May 1969. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. Annual subscription rates—United States and its possessions: institutional (multiple-reader) subscriptions,* $21.00; personal (regular) subscriptions,† $17.00; student, intern, and resident physician subscriptions,† $10.00. Canada and Mexico: institutional (multiple-reader) subscriptions, $22.00; personal (regular) subscriptions, $18.00; student, intern, and resident physician subscriptions, $11.00. Other countries: institutional (multiple-reader) subscriptions, $24.00; personal (regular) subscriptions, $21.00; student, intern, and resident physician subscriptions, $14.00. Single copies, $2.50 postpaid.

*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and all city, county, state, province, and national government bureaus and departments and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the names of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

Contents continued

American Heart Journal

JUNE 1969

Contents

continued on page 2

Contents *continued*

continued on page 7

Vol. 77, No. 6, June, 1969. American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. 63103. Annual subscription rates—United States and its possessions: institutional (multiple-reader) subscriptions,* $21.00; personal (regular) subscriptions,† $17.50; student, intern, and resident physician subscriptions,† $10.50. Canada and Mexico: institutional (multiple-reader) subscriptions, $21.50; personal (regular) subscriptions, $20.00; student, intern, and resident physician subscriptions, $13.00. Other countries: institutional (multiple-reader) subscriptions, $24.00; personal (regular) subscriptions, $22.00; student, intern, and resident physician subscriptions, $14.00. Single copies, $1.50 postpaid.

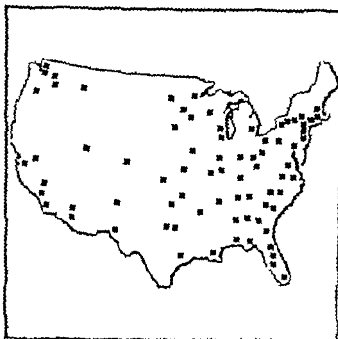
*Institutional (multiple-reader) subscriptions are available to both public and private libraries, schools, hospitals, and similar city, county, state, province, and national government bureaus and departments; and all commercial and private institutions and organizations.

†Personal (regular) subscriptions, and all student-rate subscriptions must be in the name of, and billed to, individuals.

Second class postage paid at St. Louis, Mo.

Will the guy who sells you a *sophisticated electro medical* installation still be around *when something goes wrong?*

We'll be here



And here and here and here and here and here and here and

Maybe you didn't know that Litton Industries has been a respected manufacturer of electro medical apparatus for years (in West Germany where the idea of Black Forest *craftsmanship is not yet scorned*)

Now we're introducing our proved product line into the United States. It's a more complete line than you'll find anywhere And to solve one of your basic problems before it ever comes up servicing will be handled from our already-established regional offices, nationwide

We're ready to start working with you today Phone or write us, and we'll send your nearest Litton representative You'll find him close at hand

Now and after you buy something, too

 Litton Medical Products

A Litton Industries Group Profexray Division

515 E. Touhy Avenue, Des Plaines, Ill. 60018 Telephone (312) 296-4488

Contents continued

American Heart Journal

January 1969 Volume 77 Number 1

Editorial

Bed rest, diet, nursing, and environment

G. E. Burch, M.D.
Asam U. Ansari, M.D.
New Orleans, La.

The present-day management of heart disease has become so sophisticated that the importance and value of certain simple basic therapeutic measures such as bed rest, diet, nursing care, and control of environment receive inadequate attention, consideration, and realization in management of the patient with heart disease. Over a number of years we have observed the effects of these simple therapeutic measures on patients admitted to a two-bed climatic, cardiovascular research ward at the Charity Hospital in New Orleans which are worth noting. The importance of these four therapeutic measures was evident from our observations.

Bed rest

It has been said that advice of bed rest by the physician to the patient reflects frustration due to lack of specific therapy. This is not true. Resting in bed is of much importance to the patient with heart disease. Bed rest is the most effective, simplest, and safest means of reducing the work load of the heart. It decreases heart rate, blood pressure, cardiac output, and vigor of contraction, and is conducive to spontaneous reduction in heart size, all of which reduce the work of the heart. These hemodynamic changes due to rest favor healing and tend to improve the efficiency of contraction.[1]

As early as 1872 Fothergill[2] indicated that bed rest alone can dissipate heart failure when the symptoms are mild and of brief duration. Bed rest has been the major therapeutic measure for acute rheumatic carditis in children. We[3,4] have further observed disappearance of persistent paroxysmal nocturnal dyspnea, intractable angina, massive edema, and uncontrollable hypertension from bed rest alone in many patients.

In prescribing rest we insist that our patients remain in bed and use a bedside commode only for bowel movements and when they cannot readily use a bedpan. The duration of the bed rest varies according to the severity and nature of the heart disease. This regimen of bed rest is enforced until patients notice an improvement in their symptoms or are symptom free. They are then allowed to ambulate judiciously and only after careful deliberation. Improvement certainly becomes apparent to both patient and physician within the first few days of bed rest. The practicality and value of this approach are almost identical

From the Department of Medicine, Tulane University School of Medicine, New Orleans, La.

to those of prolonged bed rest in the management of cardiomegaly of cardiomyopathies reported earlier from our laboratories.[4]

Failure of bed rest to alleviate symptoms does not necessarily devaluate its importance. It usually indicates that it is not rigidly enforced or that the diseased state is irreversible. Visits to the bathroom, getting out of bed for telephone calls, and even for short excursions in the bedroom interfere with the therapeutic efficacy of rest and certainly interrupt the prescribed absolute bed rest.

The greatest danger of total (absolute) bed rest has been claimed to be the development of thrombophlebitis and pulmonary embolism. So far we have not observed any such incident due to bed rest itself, perhaps because our patients are instructed to take deep breaths, move the lower extremities, and, when feasible, elevate the upper part of the body with a backrest.

Diet

Decreased intake of calories has been shown to lower the basal metabolic rate, blood pressure, heart rate, and cardiac output.[4] We approach the problem of diet according to particular needs of the patients. After assessing the need of salt and calories for each patient, the dietitian is asked to discuss with the patients their likes and dislikes of various foods. In this manner we attempt to make the diet as palatable and agreeable to the patients as possible. The total quantity of calories is divided equally into four or more small meals instead of three. The diet is rich in fruits and vegetables, low in animal proteins, and always free of pork and salty, fatty, greasy foods. Supplements of vitamins are given, depending upon the nutritional state of the patient. Any electrolyte imbalance is slowly and judiciously corrected by proper oral administrations whenever possible. Intravenous and all parenteral administrations are kept at a minimum and employed only when oral administrations are definitely contraindicated.

Ideal nursing care

So far, the importance of ideal, attentive nursing care has been recognized and practiced somewhat properly only in intensive care units of hospitals. On wards and even in private rooms this measure leaves much to be desired. We are of the opinion that close, quiet, thoughtful, and kind nursing care plays a most significant role in the recovery and convalescence of patients with heart disease. This type of nursing care is practiced in our special climatic ward where three nurses, competent and carefully instructed in cardiac care, attend two patients in 8 hour shifts. These nurses have been carefully trained and appraised in detail about our objectives in therapy, the needs of the sick, the importance of psychic and physical rest, and the importance of understanding, quiet, peaceful, close attention and tenderness—all to be accomplished with limited conversation with the patient. In this manner a nurse is present 24 hours per day and all the needs of the patients are not only taken care of but anticipated in advance. This, of course, requires intelligence, dedication, and constant work. Two physicians visit the patients at least twice a day and one physician is readily available at all times. This type of physician and nursing care is of great value since it minimizes the physical activities of the patients, strengthens the value of bed rest, establishes absolute confidence in the management, and, in turn, favors physical and psychic rest of the patient.

It can be argued that the nurse-patient ratio is much closer to the ideal on our special climatic ward than on most hospital wards and that with the present shortage of nursing personnel it is difficult to establish such elegant nursing practice on general wards. However, private nursing on a personal basis (1:1 ratio) may be poor when both physician and nurse fail to understand the nursing and disease problems involved. Nevertheless, ideal nursing and attention are necessary for *all* patients who require nurses. This is as true for the nonsurgical diseases as for care in the operating room where good nursing assistance is not only insisted upon but accepted as essential. Both medical and surgical illnesses can be fatal, and patients are involved in both. It is undeniable that ideal nursing is indispensable for elegant care of all patients, and surely for those with serious heart diseases whether they are accommodated in intensive care units of the hospital or not.

The physician should meet with each

nurse to explain his patients illness, personal peculiarities, and the objectives in therapy and expectations from her services. This practice must be routine and its importance cannot be overemphasized However the general practice in hospitals today is to bid the nurse the time of day ask a few questions, write a few orders quickly escape from the bedside, and then often blame the nurse for all errors and unfavorable results. It should be remembered that all nurses are not suitable for all patients The nurse must be selected to fit the personality and needs of the sick. Any other considerations are merely compromises which at times can mean the difference between recovery or death.

Environment

The environment of patients with heart disease should be tranquil It should be calm quiet, and comfortable. The number of visitors and the duration of their visits should be strictly limited A cool, comfortable air-conditioned atmosphere reduces the work of the heart.[6] In an earlier study it was reported that patients with congestive heart failure feel a sense of comfort and relaxation and their blood pressure, pulse rate, cardiac work, and congestive heart failure can be controlled with ease soon after transfer from a hot and humid to a comfortable air-conditioned ward The importance of air-conditioning the immediate environment of patients with heart disease has been stressed by us previously [7,8] The use of air-conditioned oxygen tents which completely envelop the entire patient and his mattress rather than just part of him has proved helpful in this respect, with the air-conditioning of the tent being even more helpful on hot and humid days than the oxygen itself

We do not intend to underrate the value of the cardiac glycosides, diuretics, sedatives, vasodilators, antihypertensive drugs, and other procedures in the management of heart-disease patients. However on many occasions we have encountered patients who were not helped very much by these drugs despite proper use. Patients with intractable angina, drug-resistant hypertension and recalcitrant heart failure are a few examples. We have noticed, without surprise, that such patients began responding when the four measures discussed above were given more emphasis in management. The drug-resistant hypertension soon becomes drug responsive, anginal attacks become less frequent and even disappear the recalcitrant heart failure shifts to a state which can be controlled with less difficulty and in many patients, the large dilated heart shrinks in size. Finally to illustrate the ideas discussed it may be appropriate to describe here the course of two patients.

O. B 50-year-old Negro woman, had been under "routine" treatment for hypertension, hypertensive cardiovascular disease, and angina pectoris for at least four years. She was hospitalized twice and later followed in the cardiology clinic where she was further treated by dietary restriction, antihypertensive drugs, and coronary vasodilators. Her blood pressure ranged between 180/110 and 200/110 mm. Hg despite the above-mentioned therapeutic measures, and frequent attacks of anginal episodes continued to occur She was finally admitted to our climatic ward where she received identical treatment in addition to absolute rest and kind and sympathetic nursing in an air-conditioned, comfortable, and cheerful tmosphere. Within a short period of seven days her cardiovascular status improved remarkably and her blood pressure started to decline and was 150/90 mm. Hg prior to discharge. She did not require any nitroglycerine during the entire seven-day period. At the time of discharge she was instructed carefully with regard to the continued care at home. In this manner we have been able not only to control her disease but also to reduce the frequency of clinic visits.

M W 64-year-old diabetic Negro woman, was under treatment t the medical clinic of another hospital for arteriosclerotic heart disease with functional class 4 congestive heart failure. Despite diet, insulin, cardiac glycosides, and diuretics she showed unsatisfactory response to treatment. Her pitting edema and paroxysmal nocturnal dyspnea persisted. Finally it was decided to observe her in our climatic ward. Within one week she lost six pounds in weight without the use of diuretics. Her nocturnal dyspnea disappeared and she noticed considerable physical and psychological improvement. There ere no additional special therapeutic measures employed other than those four discussed above.

Thus, it becomes obvious from these two illustrative patients how much the four factors can contribute toward better management of heart disease patients, either alone or in combination with other therapeutic measures. The importance of *proper* institution of these four factors cannot be overemphasized. All physicians should learn to employ them properly

REFERENCES

1. Burch, G. E. and DePasquale, N. P. On resting the heart, Am. Heart J. 71:422, 1966.
2. Fothergill, J. M. The heart and its diseases with their treatment, London, 1872, H. K. Lewis, p. 205.
3. Burch, G. E. and Ansari, A. Personal observations.
4. Burch, G. E., Walsh, J. J. and Black, W. C.: Value of prolonged bed rest in the management of cardiomegaly, J.A.M.A. 183:81, 1963.
5. Proger, S. H. and Magendantz, H. Effect of prolonged dietary restriction on patients with cardiac failure, Arch. Int. Med. 58:703, 1936.
6. Burch, G. E. and DePasquale, N. P. Influence of air conditioning on hospitalized patients, J.A.M.A. 170:160, 1959.
7. Burch, G. E.: Influence of hot and humid environment on the patients with coronary heart disease, J. Chron. Dis. 4:350, 1956.
8. Burch, G. E., and Ansari, A. Tropical climate, man and heart disease. In press.
9. Burch, G. E., DePasquale, N. P. and Hyman, A. L. Influence of temperature and oxygen concentrations in oxygen tents, J.A.M.A. 176:1017, 1961.

Clinical communications

Normal maturation of spatial QRS curve characteristics in early infancy

Loren E. Ainger, M.D.
*William R. Skinner, M.D.***
Memphis, Tenn.

Alteration in the geometrical configuration of the normal heart follows the successful cardiorespiratory transition from an intrauterine to an extrauterine existence. In contrast to the functional aspects of this adaptation which are usually completed within a matter of hours or days, anatomic changes follow a leisurely evolutionary course in a growing organism. Throughout infancy and childhood, therefore, the heart and circulation adapt to the changing requirements of normal growth. It has long been recognized that these changes in the cardiac generator and the changing relationships between the generator and the chest cavity are reflected with variable fidelity by the thoracic surface electrocardiogram (ECG).

Previous reports[1,2] from this laboratory have described the QRS spatial curve characteristics for a group of term normal newborn infants which were derived from digital computer analysis of corrected electrocardiographic lead recordings obtained on the first day of life. These same infants were restudied at the age of 4 months. It is the purpose of this report to describe the QRS spatial curves for this age group and to compare these curves with those derived from recordings in the newborn period.

Case material and methods

The study group from which these infants were selected has been described in detail in previous publications.[1-4] Twelve of the 13 infants of the original group were restudied; one infant was lost to follow up. Each of the 12 infants had had normal growth and development. None had had a serious illness. Each infant had no evidence of cardiovascular disease and none were anemic.

Details of recording and instrumentation have been described previously.[1,4] For each infant Frank, Schmitt SVEC III, and McFee Parungao lead recordings were obtained in succession. The Frank chest electrodes were placed at the level of the fourth costosternal junction. All recordings were obtained with the infant mildly sedated (chloral hydrate suppositories, 300 mg. per kilogram or secobarbital sodium, 1 to 2 mg.

With the technical assistance of Patrick J. Reynolds, B.S., Bill R. Campbell, and Philip R. Dean.
From the Section of Pediatric Cardiology, Department of Pediatrics, University of Tennessee College of Medicine, 860 Madison Avenue, Memphis, Tenn. 38103.
This work was supported by Grants HE-08755 and HE-09406 from the National Heart Institute, National Institutes of Health, United States Public Health Service, Bethesda, Md.
Received for publication Dec. 6, 1967.
Address: 860 Madison Avenue, Memphis, Tenn. 38103.
**This work was done during the tenure of a Postdoctoral Traineeship, HE-05303 of the National Heart Institute, National Institutes of Health, United States Public Health Service, Bethesda, Md. 20014.

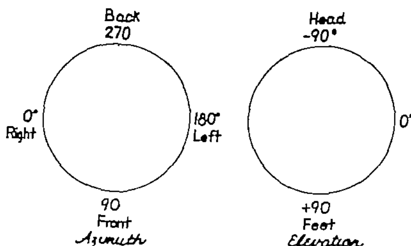


Fig. 1. Reference frame for representation of spatial orientation.

per kilogram intramuscularly). All recordings were made on ¼ inch magnetic tape at a speed of 15 inches per second. X, Y and Z lead deflections were recorded simultaneously. The analogue data was digitized at an effective rate of 947 bits per channel per second. The data was then smoothed by low pass numerical filtration.[1-4] Onset and offset of QRS were determined from visual inspection of calcomp spatial velocity plots obtained from a laboratory model computer (PDP 7 programmable data processor*).

The following rise-times were employed for QRS recognition: Frank and Schmitt SVEC III, 8 μv per millisecond; McFee-Parungao, 12 μv per millisecond. Data were then programmed as described previously on an IBM 1620 computer.[1,3]

Spatial curves were constructed by straight line connection of the arithmetic mean value for the group for each of the selected time points. Curves were constructed on both real-time and normalized time abscissae. Since the curves on each of these time bases were very similar, only curves on a normalized time base will be presented. The reference frame for spatial orientation is illustrated in Fig. 1.

Results

Spatial magnitude. In the newborn period spatial magnitude curves (Fig. 2) were characterized by 2 maxima, one occurring at the 3/10 QRS time segment and the other at the 6/10 QRS time segment. These 2 peak magnitudes were nearly equal and corresponded roughly to the maximal rightward spatial QRS vector and the maximal leftward QRS spatial vector, respectively. Spatial curves of QRS magnitude in pathologic right ventricular hypertrophy also have a similar contour. The QRS spatial magnitude curves for the same infants at 4 months of age have one peak magnitude occurring at the 4/10 time segment. *Peak magnitudes were also significantly* greater at this age ($p < 0.01 < 0.001$). Each of the 3 corrected electrocardiographic leads recorded curves of strikingly similar contour in both the neonatal period and in the 4-month-old infants although there were significant differences among them for vector magnitude representation.

Spatial velocity. Spatial velocity may be defined as the angular velocity of QRS loop sweep. Spatial velocity curves (Fig. 3) were similar in contour at both ages, peak spatial velocity occurring at the midpoint of ventricular activation. Peak spatial velocities were greater than during the newborn period. Curves recorded by each of the corrected lead systems were similar in contour.

Spatial orientation, spatial azimuth. With the exception of a significant leftward shift of the initial depolarization forces, little change occurs in the spatial azimuth (Fig

*Digital Equipment Corporation, Maynard, Mass.

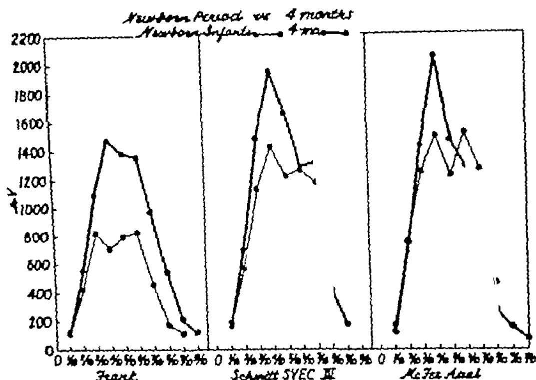


Fig. 2. Comparison of QRS spatial magnitude curves for a group of normal infants recorded t birth od at 4 months of age by the Frank, SVEC-III and axial lead systems.

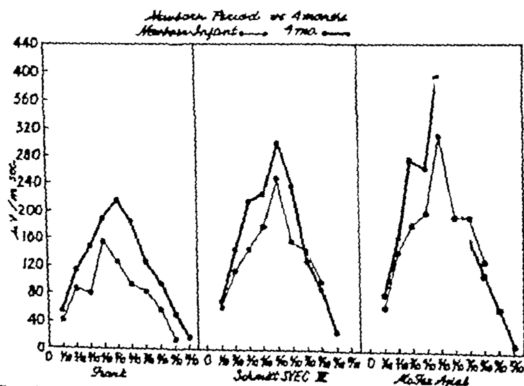


Fig. 3. QRS spatial velocity curves as recorded by the Frank, SVEC-III and axial lead systems at birth and at 4 months of age for normal infants.

Newborn Period vs 4 Months
Newborn Infants ——— 4 mo. ———

Degrees

360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0

Frank   Schmitt SVEC III   McFee Axial

Fig 4 Spatial QRS azimuth for normal infants at birth and 4 months of age recorded by the Frank SVEC III and axial lead systems.

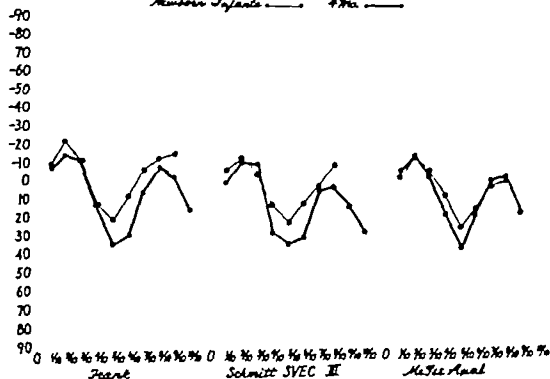


Fig 5 Spatial QRS elevation for normal infants at birth and 4 months of age recorded by the Frank, SVEC III and axial lead systems.

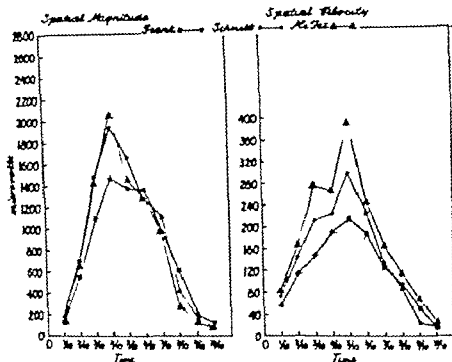


Fig 4 QRS spatial magnitude and elocity as recorded by the Frank, SVEC III and axial lead systems for normal, 1-month-old infants.

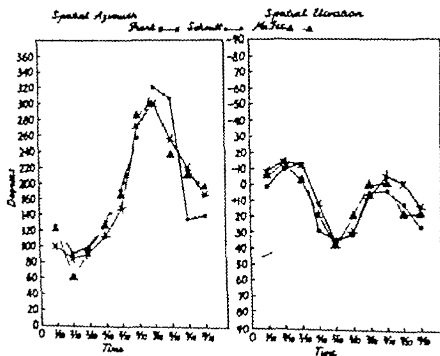


Fig 7 Comparative performance of the Frank, SVEC III and axial systems in registration of the spatial direction (azimuth nd elevation) of the successiv instantaneous QRS spatial vectors.

4) during this period of life. The anterior forces are still prominent during the initial 4/10 of ventricular activation Similar curves were recorded by each orthogonal system

Spatial elevation Changes from birth to 4 months of age are not striking although there is moderate shift of depolarization forces inferiorly during the medial third of ventricular activation (Fig 5)

Comparative performance of the 3 corrected lead systems Fig 6 illustrates the spatial curves of magnitude and velocity for the 3 lead systems displayed on the same set of axes. Spatial magnitude recorded by Schmitt SVEC and McFee Parungao net works showed close agreement while the Frank lead network recorded voltages of lesser magnitude. As was true in the new born infants, greatest spatial velocities were recorded with the McFee system and those of smallest magnitude by the Frank system whereas the Schmitt SVEC III system recorded magnitudes of intermediate values. Spatial orientations of the successive instantaneous ventricular QRS depolarization vectors were recorded in an almost identical manner by each of the 3 corrected leads an observation also true for the group during the neonatal period (Fig 7)

Discussion

Changes in spatial electrocardiographic characteristics which occur during normal growth from birth to 4 months of age can be characterized as follows an increase in spatial magnitude and peak spatial velocity a shift in the direction of ventricular depolarization forces to the left and somewhat inferiorly and persistence of anterior forces.

That spatial magnitude increase from birth to 4 months of age was not an unexpected finding since Ellison and associates[3] had reported an increase in thoracic surface cardiac potential with increasing age in infancy The causes are most likely multiple and complex. The over all increase in heart size (a larger generator with a larger dipole moment) probably plays a minor role, if any Hugenholtz and colleagues in confirmation of Brody et[10] original observation of the high conductivity (and low electrical resistivity) of intracardiac blood (160 ohm-cm. for blood 400 ohm-cm. for the myocardium) have demonstrated recently that reduction in hematocrit is accompanied by a decrease in electrical resistivity of blood which is reflected in a greater spatial magnitude of the thoracic surface potential Since the newly born infant's hematocrit approximates 50 volumes per cent as compared to the value of 36 volumes per cent at the age of 4 months, this factor alone could account for an appreciable increase in spatial magnitude. Other factors to be considered are the relationship of the heart size to the volume of the thoracic cavity[11] the geometrical relationship of the cardiac chambers to the anterior chest wall (more of the apex of the heart is occupied by the left ventricle at 4 months of age than at birth) which may determine whether spread of potential from a given region of the myocardium to the chest wall occurs in a radial or circumferential manner the degree of parallelism of the electrical field to the frontal plane of the body and the influence of phase inhomogeneities of the human thoracic contents on the thoracic surface image-space curves.[12]

Spatial velocity is in part a magnitude dependent variable. This determination represents the distance traversed in the spatial shift from an activation wave front of waning dominance to another front of emerging dominance proceeding in another direction The increase in generator size would increase the actual spatial distance covered by QRS loop sweep if all other factors remain constant, but it is doubtful that this increase in spatial velocity is a reflection of this factor

Spatial orientation of the successive-timed QRS depolarization vectors demonstrated leftward shift of early depolarization forces persistence of anterior force orientation during the initial half of activation with an inferior shift during the mid portion of depolarization. Correlation of the time sequence of these orientation changes with the spatial magnitude curves indicate that the major forces of depolarization are now directed to the left and inferiorly suggesting the normal expected emergence of electrocardiographic left ventricular dominance

Although QRS spatial curves present another view of familiar phenomena in an attractive display they present no infor

mation which is not present in the scalar ECG. In our experience, we have found that their greatest utility lies in assessment of the comparative clinical performance of several corrected orthogonal lead networks in a study group. Spatial magnitude was recorded in like manner in the 4-month-old infants by the Schmitt and McFee Parungao axial systems; this was not true during the neonatal period for this same patient group. The Frank lead network recorded lesser spatial magnitudes. Values for spatial velocity varied among each of the 3 lead networks in the same manner as in the newborn period. Each system, however, recorded the spatial orientation of the successive instantaneous depolarization forces in nearly an identical manner, as was also observed at birth.

A word of caution should be interjected concerning the extrapolation of these grouped data to the individual. For each data point, wide scatter about the arithmetic mean was apparent. This variability, in part, is due to normal individual variation of electrode placement in relation to the cardiac chambers inherent in the use of thoracic surface landmarks for their placement[2,3] and in large part due to the fact that many of the individual variables measured are not distributed in a Gaussian manner but follow a Poisson or a bimodal distribution pattern. In the latter instances the arithmetic mean is not a good centering constant, but for the purpose of this study based on a small number of patients, it was employed to present the general contour of these spatial curves for the group. What applies to the group, as a whole, therefore does not necessarily apply to any individual comprising the group.

Summary

QRS spatial curves for magnitude, velocity and orientation (azimuth and elevation) were derived by digital computer analysis of corrected lead electrocardiographic recordings obtained from 12 normal 4-month old infants. From each infant, recordings with the Frank, Schmitt SVEC III and McFee Parungao axial system were obtained in succession. These curves were compared with similar curves derived from recordings obtained on the same group of infants during the first day of life. The major changes observed were a change in contour of the spatial magnitude curve which in the neonatal period had 2 maxima to a curve with a single peak, an increase in spatial magnitude and a modest increase in spatial velocity, and a leftward shift of initial depolarization forces and an inferior shift of those forces during the middle third of depolarization. These changes reflect the expected emergence of left ventricular electrocardiographic dominance. In contrast to the ECG's of older children and adults, however, anterior forces are still dominant at this age.

Although differences in representation of spatial magnitude and velocity were observed among the 3 corrected electrocardiographic leads, orientation of successive instantaneous ventricular depolarization forces was recorded similarly by each. This suggests, that so long as one is familiar with the voltage registration characteristics of a given lead network, the choice of which one to employ is largely a matter of personal preference.

References

1. Moss, A. J., Adams, F. H., and Duffie, E. R., Jr.: Closure of the ductus arteriosus in the newborn infant, Pediatrics 32:25, 1963.
2. Ainger, L. E.: Spatial QRS curves of the newborn infant. Spatial magnitude, velocity and orientation (Frank system), Am. Heart J. 76:19, 1968.
3. Ainger, L. E.: Digital computer analysis of the vectorcardiogram of the newborn infant. Quantitative and comparative measurement of three orthogonal lead systems, Circulation 36:906, 1967.
4. Ainger, L. E.: Vectorcardiographic studies in infants and children. Comparative orthogonal lead studies in the neonatal period, Am. J. Cardiol. 21:196, 1968.
5. Anders, E. B.: An error bound for a numerical filtering technique, J. Assoc. Computing Mach. 12:137, 1965.
6. Technical Information Series Document No. 57SD340, Missiles and Ordinance Systems Department, General Electric Co., May, 1957, chap. 4.
7. Fliegelweider, E. B., and McNamee, B. J.: Filtered Sample Functions, U. S. Naval Ordinance Laboratory, Tech. Memo No. 64-104, Corona, Calif., 1965.
8. Ellison, R. C., Fischmann, E. J., and Hugenholtz, P. G.: Evidence for a progressive increase in the heart electromotive forces with body growth, Circulation (Suppl. 4) 34:96, 1966.
9. Hugenholtz, P. G., Ellison, R. C., and Nelson, C. V.: Direct studies of the effect of intracardiac

blood on the electrocardiogram II Circulation (Suppl. 4) 36:145 1967
10. Brody D A. A theoretical analysis of intercavitary blood mass influence on the electrocardiogram, Circulation Res. 4 731 1956.
11 Gamboa, R. Applicability of the axial lead system to infants and children, Am. J Cardiol. 18:690 1966.
12. Grayzel, J and Lizzi, F The combined influence of inhomogeneities and dipole location. Bipolar ECG leads in the frontal plane, Am. Heart J 74:503, 1967
13. Flaherty J T Blumenschein, S. D Spock, A, Canent, R., Gallie, T., Boineau, J P and Spach M S. Cardiac potentials in pulmonary disease. Overdistention of the lung vs. cor pulmonale (right ventricular hypertrophy) Am. J Cardiol. 20 29 1967
14 Kaneko, K., Simonson, E., and Schmitt, O H. Relationship between the position of chest electrodes (Frank nd SVEC III systems) and the anatomic position of the heart, Am. Heart J 74:58, 1967

Persistent truncus arteriosus in infancy

A study of 14 cases

Benjamin E. Victorica, M.D.
*L. Jerome Krovetz, M.D., Ph.D.***
*Larry P. Elliott, M.D.***
*Lodewyk H. S. Van Mierop, M.D.*****
*Thomas D. Bartley, M.D.*****
Ira H. Gessner, M.D.
Gerald L. Schiebler, M.D.
Gainesville, Fla.

Persistent truncus arteriosus (PTA) is a relatively rare cardiac malformation. Keith and associates[1] reported an incidence of only 0.4 per cent in 6,647 cases of congenital heart disease.

While the pathological literature has a number of well documented reviews,[2-4] only a few studies[5-11] have emphasized primarily the clinical and laboratory features. The purpose of this report is to detail the clinical observations in 14 infants with PTA and relate these to the laboratory findings.

Definition and classification

The early literature regarded most cases of "single arterial trunk" as examples of PTA. Vierordt,[12] in 1898, first separated this entity from other cardiac anomalies. The distinction between PTA and 2 other malformations with which it was frequently confused, aortic atresia and pulmonic atresia, was made by Shapiro in 1930.[13] He pointed out that in the latter 2 conditions some vestige of an atretic vessel was always present, thus demonstrating definite although unequal division of the truncus.

Lev and Saphir[3] and later Collett and Edwards, proposed that the 2 criteria necessary for the anatomic diagnosis of PTA were: (1) the presence of one arterial trunk leaving the base of the heart without any remnant of either an atretic pulmonary

From the Departments of Pediatrics, Radiology, Pathology, and Surgery and the Human Development Center, University of Florida College of Medicine, Gainesville, Fla.
Supported in part by grants from the Florida Heart Association (Statewide and Palm Beach Chapters), the Graduate Clinical Pediatric Cardiovascular Training Grant, 1-T12-HE05774-01, the Developmental Physiology Training Grant, T HD-0004 (Trainee, Dr. Victorica), and the National Institute of Health Undergraduate Training Grant, 5T1-HE5166.
Received for publication Dec. 26, 1967.
*Department of Pediatrics, Gainesville, Fla. Dr. Gessner is the recipient of an NIH Career Development Award, 1K03-HE35,143-01.
**Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Md. The recipient of a Research Career Development Award, 1 K3-HE-9761-01.
***Department of Radiology, Gainesville, Fla.
****Departments of Pediatrics and Pathology, Gainesville, Fla.; Dr. Van Mierop is the recipient of an NIH Career Development Award, 1K3-HE31,340-04.
*****Department of Surgery, Gainesville, Fla.

artery or aorta and (2) that this single arterial trunk must supply the systemic, pulmonary and coronary circulations.

Collett and Edwards[4] also divided PTA into 4 major types. Since clinically it is not possible to differentiate their Type II from Type III we will follow the classification proposed by Tandon and co-workers[9] Type I same as Type I of Collett and Edwards,[4] with the pulmonary arteries arising from the left inferior aspect of the common arterial trunk and Type II combining Types II and III with the pulmonary arteries arising close together from the dorsal wall or independently from either side of the truncus. Because of differences of opinion as to whether or not Type IV truncus[4] in which the lungs are supplied by bronchial arteries arising from the descending aorta represents a true example of PTA we have decided to exclude such cases from our series We also have excluded from our series the so-called Type V of Collett and Edwards[4] and the Type B of Van Praagh and Van Praagh [8] We feel that these types, usually without a ventricular septal defect and with 2 separate semilunar valves, are better classified as aorticopulmonary septal defects.

Material and methods

Among the cases fulfilling these criteria 14 infants, initially seen in the first year of life, were included in our study Four chest films with barium and 14-lead electrocardiograms (ECG s) were obtained in all patients. Phonocardiograms were obtained in 13 patients, using an Electronics for Medicine Research Recorder Model PR 7 They were recorded (along with respirations and Lead II ECG) at a speed of 75 mm. per second from at least 4 areas (apex, 4LICS, 2LICS and 2RICS) Cardiac catheterizations, done by a previously described technique[11] were performed in 10 patients. The diagnosis was confirmed by necropsy in 8 patients by angiocardiography in 4 and by surgery in the remaining

Table I Clinical and autopsy findings

Case No	Race	Sex	Age 1st admission	Onset CHF	Cyanosis		Growth percentiles		Systolic thrill		Ejection click
					Age onset	Degree	Wt.	Ht	Precord	SSN*	
1	W	F	7 days	5 days	Since birth	±	3	3	+	+	+
2	W	M	10 day	6 day	Since birth	±	25	50	+	0	+
3	W	M	1 mo.	9 days	Since birth	++	3	50	+	+	0
4	N	M	1 mo.	1 mo.	no	0	10	50	0	0	+
5	W	F	1 mo.	14 days	no	0	<3	<3	+	+	+
6	W	M	3 mo.	3 mo.	no	0	3	97	+	+	+
7	W	M	4 mo.	4 mo.	no	0	25	50	+	0	+
8	W	M	4 mo.	4 mo.	Since birth	±	<3	3	+	+	+
9	W	F	4 mo.	4 mo.	no	0	<3	3	0	0	+
10	W	M	5 mo	3 mo.	3 mo.	±	<3	25	+	+	+
11	W	M	6 mo	5 mo.	5 mo.	++	<3		+	0	+
12	W	M	1 day	1 day	Since birth	+	3	3	+	+	+
13	W	F	9 mo.	6 mo.	no	0	<3	<3	+	0	+
14	W	F	9 mo.	9 mo.	no	0	<3	<3	+	0	+

Abbreviations: CHF, congestive heart failure; Wt., weight; Ht., height; SSN, suprasternal notch; 3LICS, 3rd left intercostal space; 4LICS, 4th left intercostal space; Precord., precordial; Sys, systolic; Dur., duration; Loc., location; N, necropsy; A, angiocardiogram; S, surgery.
± questionable cyanosis; +, slight cyanosis; and ++, definite cyanosis.
*Split, auscultator noted 2 separate components of S_1. Intensity of murmurs on scale, I to VI.

2 (Table I) Twelve patients were of Type I and 2 patients of the Type II Seven infants (50 per cent) had some type of congenital extracardiac malformation (Table I)

One patient (Case 12) died in another hospital and no postmortem examination was performed Five patients are still alive, the oldest now being 6 years old

Results

History Only 2 patients had a family history of congenital heart disease. Case 9 had a paternal uncle and aunt with cyanotic congenital heart disease.[11] In Case 5 the mother had a normal child by a previous marriage. Since being married to the patient's father however there had been 3 further pregnancies. The first ended in a premature delivery at 6 months gestation The infant had a "split spine and died 8 hours after birth. The second child developed congestive heart failure at one month of age and by cardiac catheterization was found to have a large ventricular septal defect. Case 5 is the product of the third pregnancy

No history of cyanosis was elicited in 7 patients. Among the other 7 cyanosis was described as minimal and intermittent in 5 and moderate and constant in only 2 In 5 of these latter 7 infants cyanosis was detected at birth Six patients developed congestive heart failure in the first month of life, and the remainder around the age of 4 months Failure to thrive and frequent respiratory infections culminating in pneumonia were common (Table I)

Physical findings (*Table I*) Seven patients were below the third percentile for weight, and 3 of these were also below the third percentile for height.[12]

All 14 infants had signs of congestive heart failure on admission but even so, cyanosis was detected in only 7

A loud systolic murmur (Grade 3/6 or greater) was noted in every case. Other frequent physical findings were a prominent constant ejection click (13 cases) and a

Murmurs				S_2	*Diagnosis confirmed by*	*Truncus type*	*Associated extracardiac anomalies*
Syst	*Loc.*	*Dias*	*Loc*				
IV	4LICS	II [illegible]	3LICS	Single	N	I	
IV	4LICS	III	pex	Single	N	I	Agenesis right kidney with absent right renal artery Cryptorchidism
IV	3LICS	III	pex	Single	N	I	Congenital absence portion helix right ear
III	3LICS	I	pex	Single	N	I	
IV	3LICS	II	apex	Split*	A	I	Bilateral cleft lip and cleft palate
IV	4LICS	I	apex	Split	N	I	Congenital plasia gallbladder bilateral hydroureters with hydronephrosis
IV	4LICS	II	pex	Split	S	I	Hypospadias
continuous diast.	3LICS			Single	N	I	
III	3LICS	0	0	Single	N	I	
IV	4LICS	II	apex	Single	A	I	
IV	4LICS	0	0	Split	N	I	Chondromalacia of tracheobronchial tree with stenosis of left main stem bronchus
IV	4LICS	0	0	Single	A	I	
IV	4LICS	III	apex	Split	S	II	
IV	4LICS	I	apex	Split	A	II	Hemivertebras (T_{11} and L_4), spina bifida occulta (T and T)

lower left sternal border systolic thrill (12 cases) In 7 of these a thrill was also palpated in the suprasternal notch A diastolic murmur was noted in 11 patients. These consisted of a mid and late diastolic flow murmur maximal at the apex in 9 instances the murmur of truncal valve insufficiency in one patient (Case 1) while the remaining patient had a continuous murmur (Case 8) The second sound was noted as single in 8 patients and split in the other 6.

Laboratory findings

PHONOCARDIOGRAMS Among the 13 phonocardiograms all except one showed a characteristic pattern over the apex and fourth left intercostal space (Fig 1) Constant features included a prominent, constant ejection click and a high frequency crescendo-decrescendo or only decrescendo systolic murmur that ended before the second sound A low frequency diastolic murmur usually preceded by a summation sound was present in 11 cases.

Analysis of the second sound over the base of the heart was of particular interest. Five phonocardiograms showed a wide second sound composed of multiple components (Fig 2) In only 3 cases was the second sound single and pure. Four phonocardiograms showed 2 discrete components of the second sound and in 3 of these splitting of the second sound was seen over the second right intercostal space rather than over the left. In Case 8 the second sound was partially obscured by the continuous murmur

ELECTROCARDIOGRAMS Each of the 14 tracings had (1) a P R interval between 0.10 and 0.16 (2) a mean P vector in the frontal plane between +25 and +70 degrees (3) abnormal P waves showing right left or biatrial enlargement, and (4) a normal QRS interval Common features were a mean QRS vector in the frontal plane between +55 and +110 degrees (13/14) a deep Q wave (3 mm. or greater) in Lead III (11/14) flat, diphasic or negative T waves in V_6 (11/14) large midprecordial QRS complexes (50 mm or greater in V_4) (10/14) conduction disturbances or dysrhythmias (8/14) small (less than 2 mm.) or absent R in aVR (7/14) and a QRS-T angle greater than 45 degrees (4/14) Isolated ventricular hypertrophy patterns were unusual. Right ventricular hypertrophy was seen in 3 cases and left ventricular hypertrophy in only a single instance. Analysis of the vectorcardiograms showed that 10 patients had a clockwise QRSsÊ loop in the frontal plane. Also, 10 of 14 patients had vectorcardiographic criteria for combined ventricular hypertrophy [18]

ROENTGENOLOGIC FINDINGS

Plain Films. In each instance, the heart, lungs and upper abdominal organs were in the normal position (situs solitus) In all cases, the central and peripheral pulmonary vessels were abnormally prominent or

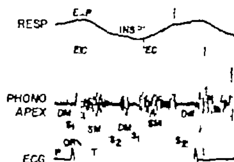


Fig 1 Phonocardiogram (Case 5) Typical findings are constant ejection click followed by a high frequency crescendo-decrescendo systolic murmur that ends before S_2 and late-diastolic flow murmur at the apex. S_1 first heart sound EC ejection click SM systolic murmur S_2 second heart sound and DM diastolic murmur

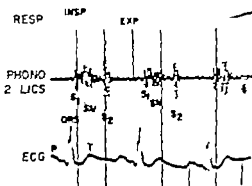


Fig 2. Phonocardiogram (Case 7). Note "wide" second sound composed of multiple closely approximated components.

the "shunt" type. Seven of the 14 patients exhibited a severe degree of pneumonia usually confined to both upper lobes. The heart was enlarged in 13 of 14 patients.

Two (both Type I) of the 14 cases showed what appeared to be a well defined pulmonary trunk. Among the remaining 12 infants, the convex density of the normally positioned pulmonary trunk was absent. This region of the upper aspect of the left heart border was either concave or simply blended into the left heart border. In 12 patients, the superior mediastinum was narrow. The right hilum appeared abnormally high in only 3 patients. The left hilum was also high in one of these infants (Type II). Six of 14 cases exhibited a *right aortic arch*. A further breakdown regarding types showed a right arch in 5 of the 12 Type I and 1 of the 2 Type II cases.

Left atrial enlargement was noted in 7 of 14 patients. In 2 others, signs of left atrial enlargement were equivocal. In all infants, the right side of the heart was abnormally prominent in either the posteroanterior (PA) or the left anterior oblique (LAO) view or both. In 3 cases, the right or anterior heart border in the LAO view was not prominent. In each of these 3 cases the common arterial trunk appeared unusually prominent.

The shape of the cardiovascular silhouette was of 2 types. The first and most common (11 of 14 cases) resembled the "egg shape" contour commonly observed in complete transposition of the great vessels. In 9 of these 11 cases, however, the upper left heart border exhibited a straighter contour than that ordinarily seen in complete transposition. In the remaining 2 cases, the left heart border was convex, and the plain films were indistinguishable from those of complete transposition of the great vessels.

The second and least common (3 cases) showed an enlarged heart with a well defined convexity along the upper left heart border. This structure resembled a large pulmonary trunk.

The left heart border in the 2 less common types of cardiac silhouette also was straight.

ANGIOCARDIOGRAPHIC FINDINGS. The procedures of choice to delineate the anatomic abnormalities in PTA are selective ascending thoracic "aortography" together with right ventriculography.

Selective thoracic ascending aortography in 8 patients revealed (1) a common semilunar valve with 2 or more cusps,

Table II. Catheterization findings

Case No.	Age at cath	Pressures (mm. Hg)						O_2 Saturation (%)			
		RV		PA		SA					
		S	ED	S/D	(mean)	S/D	(mean)	RA	RV	SA	PA
1	7 days					112/83	88	—	—	—	—
4	1 mo.	110	7	97/42	65	110/45	72	59	62	92	86
5	1 mo.	108	10			100/40	65	58	80	95	—
6	3 mo.	135	10			80/35*	75	—	68	94	—
9	4 mo.	112	12			95/60		70	69	96	—
10	6 mo.	130*	15	105/52	78	110/55	80	—	41	88	85
11	11 mo.	95	15			100/40		53	70	75	—
12	2 days	145	10					—	67	85	—
13	6 mo.	102	2	95/45	62	90/40		45	53	88	68
14	10 mo.	90	10			90/45		46	49	85	—

Abbreviations: S, systolic; ED, end-diastolic; S/D, systolic/diastolic; RA, right atrium; RV, right ventricle; PA, pulmonary artery; SA, systemic artery; and Cath, catheterization.
*Simultaneous pressures.

(2) both coronary arteries arising from the truncus (3) a large common arterial trunk with the pulmonary arteries arising from either an aneurysmal like sac to the left of the common arterial trunk (Type I) or arising in an independent fashion (Type II) and (4) incompetence of the truncal valve in one patient.

In two cases, the origin of the right coronary artery was well delineated The right coronary artery in both these cases (and the cases examined at necropsy) arose from above the right or anterior truncal cusp This was best seen in the lateral view of the aortogram The importance of this finding will be dealt with in the discussion

RIGHT VENTRICULOGRAM Right ventriculography was performed in 2 cases. In each case, the common arterial trunk and pulmonary arteries opacified simultaneously The single arterial trunk arose above a large ventricular septal defect.

Of fundamental importance was total absence of visualization of a right ventricular infundibulum. In all cases examined angiocardiographically and/or at necropsy the right ventricular infundibulum was absent. This important diagnostic sign will be discussed later

CATHETERIZATION DATA Hemodynamic data was obtained in 10 infants (Table II) Right ventricular systolic pressure was abnormally elevated in 3 patients. In 2 instances (Cases 6 and 10) simultaneous recordings from the right ventricle and from the root of the trunk showed a significant systolic pressure difference (55 and 20 mm. Hg respectively) across the common truncal valve. Right ventricular end-diastolic pressure was elevated (greater than 8 mm. Hg) in 7 cases.

Systemic arterial pulse pressure was over 40 mm Hg in 8 of the 9 patients in whom it was measured. The pulmonary artery

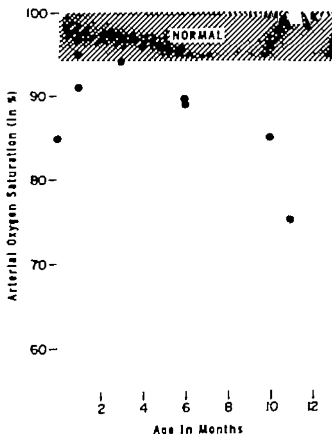


Fig 3 Systemic arterial oxygen saturation (in per cent) obtained during cardiac catheterization in nine infants with PTA. Note that in all cases except one it is greater than 85 per cent.

systolic pressure was within 10 mm. Hg to the "aortic" pressure in the 3 cases in which the pulmonary artery was entered.

An increase in oxygen saturation at the right ventricular level was observed in 3 of the 6 patients for whom the data was available. Arterial oxygen saturation was 85 per cent or greater in 8 of the 9 infants in whom it was obtained (Fig. 3). Pulmonary artery oxygen saturation was obtained in 3 instances, and ranged from 3 to 20 per cent less than systemic arterial oxygen saturation.

Discussion

The clinical diagnosis of PTA may be difficult, particularly in infancy. The broad spectrum of clinical findings described in the literature can be partially explained because in some instances patients with "end-stage" tetralogy of Fallot (pulmonic atresia with a ventricular septal defect)[17] or patients with Type IV truncus arteriosus[1] were included in the series. Types I and II present a more homogeneous clinical picture.

All physical and laboratory findings were those of a large left-to-right shunt. Early onset of congestive heart failure and frequent respiratory infections were present in all our cases. As described previously,[21, 8] marked growth retardation was a common feature.

Cyanosis has been described as a characteristic finding,[18, 21-23] but patients with a large pulmonary blood flow may have resting arterial oxygen saturations close to normal. Minimal or intermittent cyanosis has been pointed out by several groups[1, 8, 11, 13] but constant cyanosis usually does not appear until pulmonary vascular resistance increases and the pulmonary blood flow decreases.

In our series, 6 of the 7 cases with such an extracardiac anomaly had a left aortic arch (Fig. 4). The high incidence of extracardiac anomalies has been mentioned.[13, 23] Lampertico,[5] in a review of 49 cases, noted that over half the cases had some type of extracardiac congenital anomaly. The most common are absence or hypoplasia of one kidney,[4, 5, 9, 16, 25] absent gallbladder,[5, 8, 9] hypoplasia of one lung,[8, 25] and cleft palate or bony abnormalities.[1-4, 9, 24]

A common auscultatory feature was a constant prominent ejection click followed by a loud crescendo-decrescendo systolic murmur maximal along the lower left sternal border. This murmur usually ended before the second sound, in contrast to many isolated ventricular septal defects in which the systolic murmur obscures the second sound. As is usual in large left-to-right shunts, an apical flow murmur was frequently present. Murmurs of truncal stenosis, as described by Tandon and associates, were not identified as such in our series although catheterization data suggested this in 2 patients.

Continuous, machinery murmurs mimicking a patent ductus arteriosus are rare,[11, 20, 25] and it was present in only one of our cases. A diastolic murmur of truncal valve insufficiency was detected in one patient. Similar cases with truncal valve incompetence have been reported.[17]

A loud "pure" second sound over the base of the heart has been considered as characteristic.[17, 20, 21, 23] In the present series the second sound was single in 8 patients. Phonocardiographically, however, a single and "pure" second sound was seen in only 3 infants. In 5 other cases, the phonocardiogram showed a "wide" second sound composed of multiple components as described by Gasul and co-workers.[17] This probably accounts for some of the "splitting" described on auscultation. A "split" second sound comprised of 2 distinct components has been reported,[20] but such documentation is rare.[8] Four of our phonocardiograms showed 2 discrete components

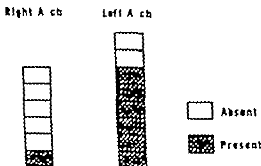


Fig. 4. Associated congenital extracardiac anomalies in relation to the side of the aortic arch in 14 infants with PTA. In all except one case, such anomalies are associated with a left aortic arch.

of the second sound. We think the two components are due to asynchronous tensing of the walls of the aorta and pulmonary arteries.[1] The cineangiogram in Case 10 showed filling and the movements associated with filling of the common pulmonary artery to be slightly later than those in the truncus.

Right axis deviation is said to be common[9,11,22] but 70 per cent of our patients had a mean QRS axis between +55 and +90 degrees. A finding not stressed previously was 1 degree A V block or a dysrhythmia in 8 of our 14 patients. A tall peaked P wave (P pulmonale) has been reported[11,22] as a most characteristic finding but was present in only 5 of our cases. The most common electrocardiographic pattern was biventricular hypertrophy. Despite some reports[9,22] to the contrary isolated left ventricular hypertrophy was seen in only one of our patients. An abnormally flat biphasic or negative T wave in V_6 was present in almost 80 per cent of our cases, in contrast to the observations of Portillo and Perez Martin[22] who frequently noted positive T waves in V_1 through V_6.

Plain film findings highly suggestive of PTA are right aortic arch occurring in a patient with prominent pulmonary arterial vascularity (50 per cent of our cases) (Fig 5) A right aortic arch is rarely seen in other congenital heart lesions with *shunt* vascularity The only other form of congenital heart disease that enters into the differential diagnosis under these same circumstances is tricuspid atresia with transposition of the great vessels. Most patients with right aortic arch are either normal or have a congenital heart lesion characterized by decreased pulmonary vascularity (e.g tetralogy of Fallot)

In patients with a *left* aortic arch the diagnosis from plain films is more difficult (Fig 6) X-rays of these patients strongly resemble those of complete transposition of the great vessels. However upon closer inspection the majority of our cases exhibited a straighter upper left heart border (Fig 6,*B*) than in complete transposition of the great vessels.

An abnormally high left hilum was present in only one patient (of the Type II variety) When present, it is a valuable sign[1] but it is uncommon in our experience.

Once PTA is suspected on the basis of a right aortic arch and shunt vascularity Type I may be distinguished from Type II by the appearance of the upper left heart border In Type I the aneurysmal like sac formed by the origin of the left pulmo-



Fig 5 PTA with shunt vascularity and right aortic arch. (A) Type I and (B) Type II The right aortic arch is obvious in (A) Case 10 whereas in (B), Case 13 it is detected by deviation of the trachea to the left (arrow). Note the relative straight line contour of the upper left heart border in both cases. If the condition PTA is being considered, the convex density in the usual position of the pulmonary trunk (arrow) indicates Type I rather than a Type II



Fig. 6 Tw cases of PTA with shunt vascularity and left aortic rch, (A) and (B) both Type I In (A), Case 7 the right hilum appears slightly higher than normal The roentgen findings in this case are not specific. In (B), Case 14 the superior mediastinum is narrow for age and the right heart is enlarged resembling the contour of complete transposition of the great vessels. Note however that the left heart border is straighter than usually seen in these cases.



Fig 7 Thoracic aortogram In Type I PTA, (A), Antero-posterior view and (B), lateral view There is dense opacification of large common arterial trunk (CT) nd single semilunar valve. In Type I the site of origin of the left pulmonary artery from the left inferior aspect of the common trunk forms an aneurysmal-like protrusion (arrows). This structure may simulate a normal pulmonary trunk in plain films.

nary artery may produce a convex density on plain films identical to a pulmonary trunk (Figs. 5,A and 7,A). In the Type II no such convex density exists because the pulmonary arteries arise independently. This pulmonary trunk sign was present in 2 cases and is only significant in the presence of a right aortic arch.

The procedure of choice to diagnose PTA is selective angiocardiography. Either selective ascending thoracic aortography and/or right ventriculography will delineate the anatomic abnormalities. If the route of catheterization is via a saphenous vein both right ventriculography and aortography may be performed. The latter is achieved since manipulation of the catheter through the truncal valve can often be accomplished.

Right ventriculography may be as valuable as thoracic aortography in arriving at the correct diagnosis. This becomes apparent when it is realized that PTA is characterized by a maldevelopment of the conus septum or outflow portion of the right ventricle. The maldevelopment of the conus septum is manifested by what appears to be *absence of a normal right ventricular infundibulum*. With right ventriculography the upper anterior portion of the right ventricle is relatively smooth and a well defined infundibulum is never visualized (Fig. 8,A).[11] In addition right ventriculography reveals a large ventricular septal defect with a single arterial trunk arising from both ventricles.

The origin of the pulmonary arteries and coronary arteries are best demonstrated by selective ascending aortography with the catheter tip just above the truncal valve. Advantages of selective aortography are that the type of PTA is more easily defined, the coronary artery pattern and the truncal valve cusps better delineated, and truncal valve incompetence, if present, revealed.

Determination of the site of origin of the right coronary artery is important. Since the common arterial trunk may be so anteriorly displaced one might be misled into thinking this is a peculiar form of transposition. The right coronary artery in PTA arises normally from the right or anterior cusp, the posterior cusp being the noncoronary one (Fig. 8,B). In all conditions characterized by transposition of both the aorta and pulmonary trunk (i.e., complete *transposition, congenitally corrected transposition*, various forms of single ventricle



Fig. 8. Angiocardiograms in 2 cases of PTA. (A), Lateral view of a right ventriculogram. There is opacification of a trabeculated right ventricle (*RV*). An angiocardiographic hallmark of PTA is absence of a well defined right ventricular infundibulum. (B), Lateral view of a thoracic "aortogram." The large common arterial trunk (*CT*) is anteriorly displaced, and under some circumstances, might be mistaken for a transposed aorta. The fact that the *origin of the right coronary (RC) is normal (arises from* above the right aortic cusp) indicates this is not a condition characterized by transposition of both great vessels.

with transposition etc.) the right coronary artery arises from the posterior cusp and the right or anterior aortic cusp is the noncoronary one.[14]

Differential diagnosis from an angiocardiographic viewpoint involves primarily aorticopulmonary window with or without a ventricular septal defect and right pulmonary artery arising from aorta with a ventricular septal defect. Angiocardiographic evidence of 2 semilunar valves and both coronary arteries arising above their respective aortic valve sinuses will usually suffice as differentiating points. If aortography is questionable, right ventriculography will differentiate these conditions. In aorticopulmonary window (with or without a ventricular septal defect) right ventriculography will reveal an infundibular chamber. As mentioned above, in PTA the infundibulum appears absent.

At cardiac catheterization the systolic pressures in the right ventricle were usually close to those of the common trunk. In 2 patients, however some degree of truncal valve stenosis was documented. The presence of a wide systemic arterial pulse pressure as seen in several of our cases has been stressed.[1,9,10,13,22] Anderson and colleagues,[11] however found normal or no diagnostic pulse pressures in their series. Similar wide systemic pulse pressure was documented at catheterization in patients with isolated patent ductus arteriosus and in patients with patent ductus arteriosus associated with a ventricular septal defect (Fig. 9). The wide pulse pressure reflects the aortic run-off that is common to all 3 entities. For that reason, a wide pulse pressure cannot be used as a differential point in distinguishing between a patent ductus arteriosus and PTA as suggested by Gasul and associates.[19]

The pulmonary artery oxygen saturation was less than systemic oxygen saturation (in Case 13 by almost 20 per cent) in the 3 patients in which the pulmonary artery was entered. This interesting finding which has been observed in other series,[9,11] is due to preferential streaming of blood leaving

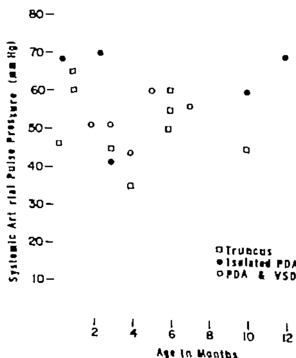


Fig. 9. Systemic arterial pulse pressures in infants with PTA, isolated patent ductus arteriosus, and patent ductus arteriosus with ventricular septal defect. (Data obtained at cardiac catheterization.) Note similar pulse pressure in all these conditions.

the 2 ventricles. Thus, the left ventricle preferentially ejects its blood through the truncus into the aorta and the right ventricle into the pulmonary arteries.

Summary

Infants with PTA (Types I and II) usually have growth retardation and the physical findings of a large left-to-right shunt. Cyanosis is almost always either absent or minimal. Characteristically a loud systolic murmur along the left sternal border is present. It is preceded by a prominent constant ejection click and ends before the second sound. A diastolic flow murmur is frequently present at the apex. Continuous or truncal valve insufficiency murmurs are rare. 'Splitting' of the second sound is not uncommon. This auscultatory finding may be explained because, in some patients, the second sound is 'wide,' being composed of several closely approximated or indeed 2 discrete components. The ECG usually shows atrial enlargement, a mean QRS axis between +55 and +110 degrees, combined ventricular hypertrophy, and abnormal T waves in V_1. Isolated right or left ventricular hypertrophy is rare.

A high incidence of extracardiac anomalies is found especially in patients with a left aortic arch. The typical roentgen findings are prominent vascular markings of the shunt type in a patient with right aortic arch (50 per cent of our cases). The plain film findings in patients with left aortic arch are similar to those with complete transposition of the great vessels except that they have a straighter upper left heart border. Selective angiocardiography either with the catheter in the root of the trunk or in the right ventricle is the best diagnostic procedure to delineate the anatomic abnormalities. Absence of the right ventricular infundibulum with a single arterial trunk arising from both ventricles are the diagnostic features. At cardiac catheterization the systemic arterial pulse pressure is generally wide reflecting the aortic run-off lesion. Systemic arterial oxygen saturation approaches normal in many of these infants. Differences in oxygen saturations between the pulmonary arteries and the ascending aorta" are most likely due to preferential streaming.

REFERENCES

1. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, New York, 1967, The Macmillan Company.
2. Humphreys, E. M.: Truncus arteriosus communis persistens. Criteria for identification of the common arterial trunk, with report of a case with four semilunar cusps, Arch. Path. 14:671, 1932.
3. Lev, M., and Saphir, O.: Truncus arteriosus communis persistens, J. Pediat. 20:74, 1942.
4. Collett, R. W., and Edwards, J. E.: Persistent truncus arteriosus. A classification according to anatomic types, Surg. Clin. North America 29:1245, 1949.
5. Lampertico, P.: Persistent truncus arteriosus communis. Review of the literature and presentation of 49 cases of true truncus arteriosus and 18 examples of related conditions, Folia Hered. Path. 14:Suppl. IV, 1964.
6. Van Praagh, R., and Van Praagh, S.: The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases, Am. J. Cardiol. 16:406, 1965.
7. Manhoff, L. J., Jr., and Howe, J. S.: Absence of the pulmonary artery: A new classification for pulmonary arteries of anomalous origin. Report of a case of absence of the pulmonary artery with hypertrophied bronchial arteries, Arch. Path. 48:155, 1949.
8. Moragues, V.: Cardiac anomalies with a single arterial trunk, Bull. Internat. A. M. Mus. 31:65, 1950.
9. Tandon, R., Hauck, A. J., and Nadas, A. S.: Persistent truncus arteriosus. A clinical, hemodynamic, and autopsy study of nineteen cases, Circulation 28:1050, 1963.
10. McCue, C. M., Lester, R. G., Bosher, L. H., Jr., and Mauck, H. P., Jr.: Persistent truncus arteriosus. A clinical correlation with the pathologic anatomy, Dis. Chest 46:507, 1964.
11. Anderson, R. C., Obata, W., and Lillehei, C. W.: Truncus arteriosus. Clinical study of fourteen cases, Circulation 16:586, 1957.
12. Vierordt, H.: Die angeborenen Herzkrankheiten. Unvollstandige Theilung und einseitige Umbildung des primaren Truncus. Persistenz des Truncus arteriosus, Specielle Pathologie und Therapie, Nothnagel 15:132, 1898.
13. Shapiro, P. F.: Truncus solitarius pulmonalis. A rare type of congenital cardiac anomaly, Arch. Path. 10:671, 1930.
14. Krovetz, L. J., McLoughlin, T. G., Mitchell, M. B., and Schiebler, G. L.: Hemodynamic findings in normal children, Pediat. Res. 1:122, 1967.
15. Stuart, H. C.: Percentile charts for measurements of boys and girls—derived from longitudinal studies of child health and development conducted at the Harvard School of Public Health between 1930 and 1950, Pediatrics, Suppl. 24:875, 1959.
16. Elliott, L. P., Taylor, W. J., and Schiebler, G. L.: Combined ventricular hypertrophy in infancy. Vectorcardiographic observations with

special reference to the Katz-Wachtel phenomenon, Am. J Cardiol. 11:164 1963
17 Taussig, H B. Clinical and pathological findings in cases of truncus arteriosus in infancy Am. J Med. 2:26, 1947
18. Kroetz, L. J Gemoer L H., and Schiebler G. L Pediatric cardiology New York, Hoeber Medical Division, Harper & Row Publishers Inc., in press.
19 Roos, A.: Persistent truncus arteriosus communis. Report of case with four semilunar cusps and aortic arch on the right side Am. J Dis. Child. 50:966, 1935.
20. Rowe, R. D and Vlad, P Persistent truncus arteriosus Report of two cases with right aortic arch, AM. HEART J 46:296, 1953
21 Gasul, B. M., and Marienfeld, C. J Symposium on cardiovascular diseases. Clinical diagnosis of the cyanotic types of congenital malformations of the heart, Pediat. Clin. North America 1 131 1954
22. Armer R. M DeOliveira, P F and Lurie P R. The truncus arteriosus Review of seventeen cases and report of surgery in seven patients, Circulation 24:878, 1961
23. Nadas, A. S Pediatric cardiology ed. 2, Philadelphia, 1963, W B. Saunders Company p. 505.
24. Fontana, R. S., and Edwards, J E. Congenital cardiac disease A review of 357 cases studied pathologically Philadelphia, 1962, W B. Saunders Company
25. Beaver D C. Persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, Arch. Path. 15:51 1933.
26 Campbell, M and Deuchar D C. Continuous murmurs in cyanotic congenital heart disease, Brit. Heart J 23 173, 1961
27 Deely W J Hagstrom, J W C., and Engle M A. Truncus insufficiency: Common truncus arteriosus with regurgitant truncus valve. Report of four cases, AM. HEART J 65:542, 1963.
28. Morgan, A. D Brinsfield, D and Edwards, F K.: Persistent truncus arteriosus An unusual variant with atresia of the aortic arch Am. J Dis. Child. 109 71 1965.
29 Gasul, B M Arcilla, R. A., and Lev M Heart disease in children. Diagnosis and treatment, Philadelphia, 1966, J B. Lippincott Company
30. Singleton, E. B., McNamara, D G., and Cooley D A.: Retrograde aortography in the diagnosis of congenital heart disease in infants, J Pediat. 47 720, 1955.
31 Goldberg, M J and McGregor M Persistent truncus arteriosus Report of a case with atypical radiologic features, AM. HEART J 55:360, 1958.
32 Portillo, B. and Perez Martin, R. Tronco Arterioso Comun—Estudio electrocardiografico en 17 casos, Arch. Inst. Cardiol. Mex. 30:609 1960.
33. Gleason, D C., Ferguson, T., Hartmann, A. F., Jr and Elliott, L. P : Angiocardiographic differentiation between Fallot pulmonary atresia and type IV persistent truncus arteriosus, Am. J Roentgen. 100:312, 1967
34 Elliott, L. P Amplatz, K., and Edwards, J E.: Coronary arterial patterns in transposition complexes. Anatomic and angiocardiographic studies, Am. J Cardiol. 17:362, 1966

Histology of papillary muscles of the left ventricle in myocardial infarction

*Frank R. Brand, M.D.**
*Arnold L. Brown, Jr., M.D.***
*Kenneth G. Berge, M.D.****
Rochester, Minn.

The relatively common occurrence of scarring of the papillary muscles of the left ventricle in hearts with and without myocardial infarction has concerned pathologists and clinicians alike since the early part of this century. This prevalence has been variously reported as 25 to 60 per cent in consecutive autopsy series.[1,2] The nature of this problem is of more than academic interest. If the scarring which occurs in these muscles subsequent to acute infarction cannot be distinguished from that unrelated to coronary arterial disease, then study of papillary muscle damage in healed myocardial infarction is impossible. This would necessitate study of papillary muscle damage limited to hearts with acute myocardial infarction and would bias such a study toward the minority of infarctions in which the outcome was fatal. Two important works have added valuable information to this subject. Amenomiya[1] reported 11 instances of scarring of the papillary muscles in hearts without coronary atherosclerosis. He was impressed with the abnormal appearance of the small arterioles in these papillary muscles; the arteriolar changes included marked thickening of vessel walls with intimal hyperplasia and hyaline degeneration. Schwartz and Mitchell[2] reported on lesions of the myocardium occurring in a random sample of hospital autopsies. They reported frequent scarring of the papillary muscles and, more importantly, noted 2 patterns of fibrosis, one related to disease of the small arterioles and the other occurring only in hearts with large myocardial scars. In their 137 cases, 21 specimens had large myocardial scars. The prevalence of the pattern of papillary muscle fibrosis occurring with large myocardial scars was not reported. In that study, the right ventricular papillary muscles were rarely abnormal.

The occurrence of disease of the small vessels in the papillary muscles has many interesting aspects. It is reported to be unrelated to arteriolar disease elsewhere in the body as seen, for example, with hypertension or diabetes mellitus.[2] This is suggestive of the arteriolar degeneration

From the Mayo Clinic and Mayo Foundation; Section of Experimental and Anatomic Pathology and of Medicine, Mayo Graduate School of Medicine, University of Minnesota.
Read at the meeting of the American Heart Association, San Francisco, Oct. 20 to 21, 1967.
Received for publication Feb. 7, 1968.
*Resident in Medicine, Mayo Graduate School of Medicine, University of Minnesota.
**Section of Experimental and Anatomic Pathology, Rochester, Minnesota.
***Section of Medicine, Rochester, Minnesota.

January 1969 Vol. 77 No. 1 pp 26-3

better known in canine hearts.[4] This process is reported to be age-dependent in man and in dogs.[3,4]

The occurrence of acute infarction of the papillary muscles as seen in autopsy series has been reported in both the English and the Russian literature. The prevalence of acute infarction of one or both papillary muscles in a series of 420 consecutive autopsies from a Veterans Administration hospital has been reported as 3.8 per cent. This series was not limited to cases of myocardial infarction.[1] In 2 of 4 studies of the prevalence of acute necrosis of the papillary muscles in acute fatal myocardial infarction, a prevalence of 20 per cent was reported [7] while in the others the presence of acute papillary muscle necrosis was reported in 50 per cent of the cases.[5] There is enough variation in these data to suggest a need for additional studies.

The present study was designed to compare a series of hearts with evidence of myocardial infarction to appropriate controls without evidence of myocardial lesions in an attempt to evaluate the histologic patterns of fibrosis of the left ventricular papillary muscles.

Materials and methods

The autopsy records and preserved hearts of patients with healed or acute myocardial infarction who came to autopsy in the Section of Pathologic Anatomy of the Mayo Clinic, were utilized in this study. Clinical records, available in all but 10 cases in which death occurred outside the hospital, were reviewed. Selection of cases was on a pathologic rather than a clinical basis and all myocardial scars exceeded 2.0 cm. in at least one dimension. Only residents of Rochester, Minn., were included so that the experience in a midwestern community of 30 000 people could be evaluated. The years 1950 through 1953 were chosen during which time most of the medical care of the community was provided by the Mayo Clinic. The autopsy rate during these years was 70 per cent for deaths of Rochester residents occurring within and outside the hospital, and all autopsies were done by the Section of Pathologic Anatomy of the Mayo Clinic. Control groups were selected from the same autopsy population during the years of the study in a consecutive fashion according to desired criteria (that is, absence of myocardial infarction and degree of coronary atherosclerosis).

Four sections were taken from each heart for microscopic study. Cross sections of the anterior and posterior papillary muscle of the left ventricle were obtained from the midportion of the muscle belly proximal to the origin of the chordae tendineae. Sections were also taken from the left ventricular myocardium at the base of each papillary muscle. The microscopic findings were assessed and recorded without knowledge of the gross anatomic or clinical data. Presence and extent of acute infarction were recorded. Fibrosis and extent of small vessel disease were graded as absent, present, or marked in a manner to be comparable with previously reported studies.

A search of the autopsy records disclosed 143 cases of old and recent myocardial infarction in local residents within the 4 years studied. From this group, 5 cases were rejected because other conditions were present which could interfere with the pattern of lesions or the clinical manifestation of ischemic papillary muscle damage (2 cases of subacute bacterial endocarditis and 3 cases of rheumatic mitral valvular disease). Five other cases were eliminated because the pathologic specimens were unsatisfactory for study. A total of 133 cases remained. Seventy

Table I. Distribution of lesions of the papillary muscles according to histologic appearance in 133 hearts with myocardial infarction

Histologic appearance	N		Per cent of 133	
Normal	26		20	
Fibrosis, total	107		80	
Focal only		27		20
Diffuse only		45		34
Both		35		26
Acute infarct†	18		14	

*Cases in which specific area of focal fibrosis occurred in muscles generally involved with diffuse fibrosis.
†Cases represented also in the above categories.

nine patients were men and 54 were women and the average age was 71 years (range 34 to 94).

Results

The cross sections of the papillary muscles could be classified into 4 groups on the basis of histologic appearance: normal, 2 distinctive patterns of fibrosis, and acute infarction (Table I). Both the anterolateral and the posterior papillary muscles were normal in 20 per cent of specimens (Fig. 1,A). This illustration shows closely knit muscle fibers separated into bundles by thin sheets of connective tissue. A pattern of papillary muscle fibrosis termed "focal" is shown in Fig. 1,B. The prevalence of this pattern, either alone or with diffuse fibrosis, in one or both papillary muscles in this series was 46 per cent and it is this appearance of fibrosis that Schwartz and Mitchell[3] found only in hearts with large myocardial scars. This focal fibrosis is characterized by (1) large areas of amorphous collagen tissue, (2) sparing of muscle fibers in perivascular and subendocardial areas, and (3) no association with disease of the small vessels. The other histologic form of fibrosis is termed "diffuse" (Fig. 1,C). The prevalence of this pattern, alone or with focal fibrosis, was 60 per cent in this series. The diffuse pattern of fibrosis is characterized by (1) strands of fibrous tissue which intermingle with muscle fibers, (2) prominent fibrosis of subendocardial and perivascular areas, and (3) association with degenerative disease of the arterioles. For completeness, it should be mentioned that the 2 histologic patterns of papillary muscle fibrosis were usually distinct, but in a few cases they were not typical. An example of this is shown in Fig. 1,D where the subendocardial and perivascular sparing of muscle fibers seen in focal fibrosis is combined with intermingling of fibrous tissue and disease of the small vessels characteristic of the diffuse pattern. The over-all prevalence of some form of fibrosis of one or both papillary muscles in this series was 80 per cent.

The relationship of these patterns of fibrosis of the papillary muscles to myocardial infarction was studied by comparing this series to control groups similar in age and sex distribution but without evidence of myocardial infarction. The control group was further subdivided into those with moderate and those with severe coronary artery disease. The distribution of papillary muscle fibrosis in study and control groups is marked by the absence of the focal pattern in control groups (Table II). The association of the focal pattern of fibrosis with myocardial infarction is significant ($P > 0.01$). There is no such association between diffuse fibrosis in the papillary muscles and myocardial infarction. A papillary muscle was usually not totally involved by acute infarction or focal scarring. The extent of damage in terms of cross-sectional areas of the papillary muscles by the focal form of fibrosis formed a spectrum (Table III). Frequently large areas were involved, 50 to 75 per cent as determined from total cross-sectional area if 2 or more bellies composed the muscle. Distribution of the diffuse pattern of fibrosis was rarely massive.

The relationship between types of papillary muscle fibrosis and disease of the small vessels was studied. A contingency table comparing the diffuse pattern of fibrosis with disease of the small vessels indicates a clustering about the diagonal of correlation and an absence of cases in the cells of poor correlation—upper right and lower left (Table IV). Evaluation of these data by the chi square test confirms a significant relationship between diffuse fibrosis and disease of the papillary muscle arterioles ($P < 0.01$). A similar comparison of the focal form of fibrosis and disease of the small vessels revealed no significant relationship indicated by the presence of many cases in cells of poor correlation (Table V). Study of other disease entities in this series known to be associated with disease of small vessels (namely, diabetes mellitus and hypertension) revealed no evident association between these diseases and the prevalence of arteriolar disease in the papillary muscles.

The histologic appearance of acute infarction of a papillary muscle is shown in Fig. 1,E. The infiltration of polymorphonuclear cells indicates a duration of 24 to 48 hours.[11] In this series of acute and healed myocardial infarction, the prevalence of acute necrosis of the papillary



Fig. *1.* Sections of papillary muscle stained with hematoxylin and eosin (X30). *A*, Normal. *B*, Focal fibrosis. C, Diffuse fibrosis. *D*, Mixed fibrosis. *E*, Acute infarction.

Table II. Prevalence of histologic lesions of left ventricular papillary muscle in control hearts and hearts with myocardial infarction

Lesion of papillary muscle	*Control (no myocardial infarction)*				*Myocardial infarction (133 cases)*	
	Coronary atherosclerosis					
	Moderate (15 cases)		*Marked (15 cases)*			
	N	*% of 15*	*N*	*% of 15*	*N*	*% of 133*
Acute infarction	0	0	0	0	19	14
Fibrosis						
Focal	0	0	1	6	62	46
Diffuse	10	67	13	87	80	60
Disease of small vessels	9	60	12	80	80	60

Table III. Extent of focal fibrosis of left ventricular papillary muscles in myocardial infarction

Site of papillary muscle fibrosis	*Total cases*	*Extent of papillary muscle fibrosis*			
		0 to 25%	*25 to 50%*	*50 to 75%*	*75 to 100%*
Anterolateral (cases)	35	7	7	14	7
Posterior (cases)	51	8	15	18	10

muscles was 14 per cent. When only specimens with acute mural lesions were considered, the prevalence of acute papillary muscle infarction was 33 per cent (14 of 43 specimens).

Comment

The significant association of the focal pattern of papillary muscle fibrosis with myocardial infarction strongly suggests that this pattern is the result of prior acute infarction of the papillary muscle. The histologic appearance of acute infarction of the papillary muscle is that of large areas of seemingly total necrosis of muscle fibers similar in area and location to the large amorphous areas present in the focal form of fibrosis. The variability in the extent of replacement of the papillary muscles by the focal pattern of fibrosis is consistent with the variability noticed in the small number of acute infarcts of the papillary muscle in this series. This is in sharp contrast to the usual concept of massive necrosis of the papillary muscles and may provide an anatomic basis for the transient nature of some mitral murmurs associated with acute myocardial infarction.

Disease of the small intramural vessels has been associated with aging both in man and in animals.[3,4] Both patterns of fibrosis described above are associated closely with factors that increase in prevalence with age, namely, myocardial infarction and disease of the small vessels. It is, therefore, not surprising that there are cases in this series in which both diffuse and focal patterns of fibrosis occur in a single specimen.

Disease of the small vessels of the papillary muscles is perhaps more familiar to investigators of canine vascular lesions

Table IV. Relationship of histologic diffuse fibrosis of left ventricular papillary muscle to disease of small vessels

Disease of small vessels	Diffuse fibrosis			Total
	Absent	Present	Marked	
Absent	42	10	0	52
Present	11	61	2	74
Marked	0	4	3	7
Total	53	75	5	133

Table V. Relationship of histologic focal fibrosis of left ventricular papillary muscle to disease of small vessels

Disease of small vessels	Focal fibrosis			Total
	Absent	Present	Marked	
Absent	23	14	14	51
Present	44	22	9	75
Marked	4	2	1	7
Total	71	38	24	133

although also poorly understood. Disease of the small intramural myocardial arteries is not uncommon in dogs and it is most prevalent in, but not limited to, the papillary muscles of the left ventricle. In dogs hearts, minute areas of muscle necrosis have been found in association with disease of the small arterioles. The myocardium of canine hearts with disease of the small vessels is marked by scattered small areas of fibrosis. These observations suggest that the diffuse type of fibrosis seen in human papillary muscle, related to disease of the small vessels is the result of a piecemeal process which is different from the usual concept of acute infarction. The basis of the predilection of papillary muscles to small vessel disease and diffuse fibrosis is even more conjectural. It could be related to the great stress on the papillary muscles during their physiologic performance,[7] or it could be a function of ischemia of the papillary muscles during ventricular systole that is probably of longer duration than that of the subendocardial tissue.

The presence of acute infarction of one or both papillary muscles in 33 per cent of the hearts with acute *mural* lesions makes the malfunction of these structures a reasonable explanation for many mitral murmurs in myocardial infarction. The higher prevalence of acute papillary muscle infarction reported by Heikkilä (50 per cent) could be a result of difference in selection of cases. The *present* study based on an autopsy series, was not limited to hospitalized patients and included cases in which myocardial infarction was not necessarily the primary cause of death. The series by Heikkilä[3] selected on the basis of acute fatal myocardial infarction, was perhaps not typical of all acute infarctions, fatal and nonfatal.

Summary

Study of the histology of the papillary muscles in a consecutive autopsy series of cases of acute and healed myocardial infarction revealed frequent fibrosis of these structures. Two patterns of fibrosis were identified. One termed focal was interpreted as healed acute papillary muscle infarction. The other termed diffuse, was associated with disease of the small vessels. The prevalence of acute infarction of these structures in hearts with both acute and healed mural lesions was 14 per cent. When only hearts with acute mural lesions were considered the prevalence of acute papillary muscle infarction was 33 per cent.

REFERENCES

1. DePasquale, N. P., and Burch, G. E.: The necropsy incidence of gross scars or acute infarction of the papillary muscles of the left ventricle, Am. J. Cardiol. 17:169, 1966.
2. Schwartz, C. J., and Mitchell, J. R. A.: The relation between myocardial lesions and coronary artery disease. I. An unselected necropsy study, Brit. Heart J. 24:761, 1962.
3. Amenomiya, R.: Über die Beziehungen zwischen Koronararterien und Papillarmuskeln im Herzen, Virchows Arch. path. Anat. 199:187, 1910.
4. Luginbühl, H., Jones, J. E. T., and Detweiler, D. K.: The morphology of spontaneous arteriosclerotic lesions in the dog. Roberts, J. C.,

Jr and Straus, R., editors Comparative atherosclerosis, New York, 1965 Hoeber Medical Division, Harper & Row Publishers, Inc., p 163.

5. Luginbühl, H., and Detweiler D K. Cardiovascular lesions in dogs, Ann. New York Acad. Sc. 127:517 1965

6. Nezlin, V E. and Shamesova, L. G Infarction of papillary muscles Clinical and anatomicopathologic observations, Klin. med. 29:51 1951

7 Vigoda, P S. Torn muscle often follows infarction, Med. World News 7:16, 1966.

8. Arkhangel'skii, A. V On changes of the papillary muscle of the heart in myocardial infarct, Arkh. Pat. 21:48, 1959

9 Heikkila J Mitral incompetence complicating acute myocardial infarction, Brit. Heart J. 29:162, 1967

10. Mallory G. K., White, P D and Salcedo-Salgar J The speed of healing of myocardial infarction: A study of the pathologic anatomy in seventy-two cases, Am. Heart J 18:647, 1939

11 Burch, G. E., and DePasquale N P Time course of tension in papillary muscles of heart, J.A.M.A. 192 701 1965

Vectorcardiographic and electrocardiographic manifestations of increasing left ventricular pressure overload

W. N. Powell, M.D.*
R. L. Ratney, M.D.
A. C. Witham, M.D.
J. H. Edmonds, Jr., M.D.
Augusta, Ga.

Indications for surgery are often unclear in the relatively asymptomatic patient with aortic stenosis (AS). Those with severe obstruction may have few or no symptoms, show equivocal evidence of left ventricular hypertrophy (LVH) by roentgenographic examination and have no physical findings that consistently distinguish them from those with mild obstruction.[1]

Left heart catheterization is a direct and reliable method of determining the severity of the obstruction. Because of the risk, limitation of facilities, and expense however there is some reluctance to advise it in the patient without symptoms or striking physical findings. A safe, reliable inexpensive method of estimating the degree of obstruction would therefore be extremely valuable.

Although the standard electrocardiogram (ECG) in AS may be abnormal,[2-4] the changes are said to correlate poorly both with the degree of LVH and hemodynamic findings.[1-3] Braunwald and associates found that neither precordial QRS voltage,[1] QRS axis, nor repolarization changes reflected the severity of obstruction in 100 patients with congenital AS. Patients with severe obstruction and normal precordial voltages as well as those with insignificant gradients and markedly elevated voltages were noted.

The apparent failure of the ECG to be altered predictably by various degrees of AS may be due to a lack of linear relationships between pressure, hypertrophy and voltage, the inability of the lead system to reflect these changes, or to improper selection of quantitative criteria. If such relationships exist, a corrected orthogonal lead system might be superior since theoretically it would reduce the influence of such variables as body build, electrode placement, and eccentricity of the cardiac dipole. The purpose of this study was to determine whether quantitative analysis of such a system displayed in scalar or

From the Division of Cardiology, Department of Medicine, Eugene Talmadge Memorial Hospital, Medical College of Georgia, Augusta, Ga. 30902.
Supported in part by the United States Public Health Service Research Grant No. HE 07264.
Received for publication March 8, 1968.
*Dr. Powell held a Georgia Heart Association Fellowship in Cardiology 1965 to 1966.

vectorcardiographic form might correlate sufficiently well with hemodynamic findings to allow prediction of severity. Certain measurements from the standard ECG were included for comparison.

Method

A total of 22 patients with left ventricular outflow obstruction due to AS[6] or coarctation of the aorta[7] were studied. Patients with significant mitral valve disease, more than minimal aortic insufficiency, complete left bundle branch block, or severe congestive heart failure were excluded. Left and right heart catheterizations were performed in each patient. Pressures were recorded through Statham strain gauges with the recording base line at the level of the midaxillary line. The left ventricle was intubated either by retrograde transvalvular or transseptal technique. All patients were lightly sedated with meperidine and Phenergan but were awake during recording of pressures. Although numerous hemodynamic values, such as ejection time, tension time index, stroke index, etc., were measured or calculated, the best correla-

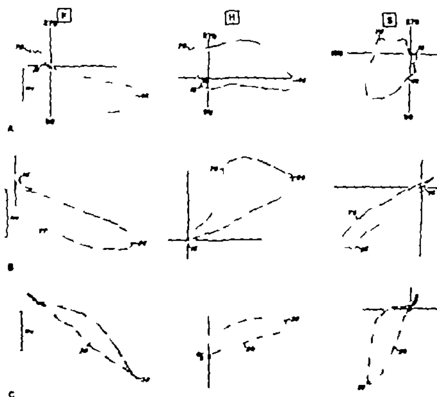


Fig. 1. Loops from 3 patients selected to show stepwise development of pattern of pressure overloading of the left ventricle. The top set illustrates the angular reference frame for recording position of vectors. It reads clockwise from 0 to 360 degrees in each plane. Frontal, horizontal, and sagittal projections are from left to right and loops are interrupted at 4 msec. intervals. Direction of transcription is indicated by the sharp end of the commas. The digits refer to the time of appearance of Q, R, 20 msec., or S vectors. P and T loops have been partially eliminated. Detailed measurements are in Table I. Regardless of LV pressure, position of the loops is approximately the same. QRS duration is shortest in the patient with the highest pressure.

A, Case 4. LVP = 174 mm. Hg. Increased voltage of R. Configuration is unaltered due to normal position of Q, R, and S vectors. *B*, Case 8. LVP = 190 mm. Hg. Increased voltage of R and S. Q is directly anterior and of low voltage. Table I indicates that the latter finding is common. Configuration is abnormal because of the posterior position of R, the leftward S, and the narrow angle between them. Anterior forces are small and their duration is only 22 msec. *C*, Case 19. LVP = 240 mm. Hg. Voltage of R is increased, most strikingly in the frontal plane. There is further evolution of angular relationships. Neither Q nor S can be identified, presumably having shifted left and into the body of the loop. Although there was no evidence clinically or at operation for myocardial infarction, there are no anterior forces.

tions were with *left ventricular pressure* (LVP) and peak systolic gradient (VG) and only these are reported.

Standard 12-lead ECG's and vectorcardiograms (VCG's) using the Helm sponge-grid electrode system[9] were obtained on each patient within a few days of the catheterization study. Scalar X, Y and Z leads were also recorded.

The nomenclature and method of quantitation of the VCG have been described previously.[7,8] Briefly, Q is the first major vector identified, R is that vector directed to the most leftward point, and S is the first major deflection after R. A major deflection is defined as a change in direction of transcription of at least 75 degrees in 2 or more planes. The maximal vector (M) in each plane, the maximal spatial vector (M) and characteristics of the 20 msec. vector were also measured. Frontal, horizontal and right sagittal plane (fp, hp, and sp) projections were recorded. Angles were noted on the reference system devised by Helm[9] which is illustrated in Fig. 1.

A number of VCG and ECG variables were initially scanned by a computer program for correlations with hemodynamic data: the spatial voltage of the 3 vectors, their position and voltage in each plane, their time of appearance, the angles formed by pairs of the major vectors in each plane, and the duration of the QRS loop and anterior forces. From the orthogonal leads, the voltage of the R wave in X, S in Z, and either the R or S in Y (whichever was greater) was measured. From the ECG, the voltages of S_{V1}, R_{V} ... R or S in aV_F (whichever was greater) and combinations of their sums, were examined. Measurements of S-T segments and T waves were not considered reliable since 10 patients were taking digitalis at the time of the study.

Results

Table I lists the patients according to LVP. Age, gradient, and the most important VCG and ECG measurements are recorded. The 2 patients whose VG was not measured were those with coarctation of the aorta. In calculation of means and standard deviation for voltages, zero values were included for voltage (when Q and S vectors could not be identified) but were excluded for angles. When S could not be identified, however, it was considered to have merged with R and ∠R-S_{hp} designated 0. For rough comparisons, mean values of the VCG of normal young adults are also listed.[8] Table II lists the highest coefficients of correlation between LVP or VG and electrical measurements. When Q_{hp} could not be identified it was considered to have moved so far to the left that it had merged with the R loop. This was found to be expressed best numerically by assigning it an extreme leftward position, i.e., 0 degrees. If r did not reach the 5 per cent level of significance it was recorded as zero.

VCG. Significant linear correlation was found between LVP or VG and the spatial voltage of the R (R_s) and maximum vectors (M_s) (Fig. 2). In all but 2 cases, M_{fp} was the frontal plane projection of M_s, i.e., they represented the same point in the spatial VCG. In all but 6 cases, M_s and R were the same.

The spatial voltage of the S vector, when identifiable, and the voltage of its projection on the frontal plane also correlated with gradient ($p < 0.01$) but not significantly with LVP. The position of R in the frontal plane ($\angle R_{fp}$) showed no correlation with pressure or gradient and no deviation from that of a population of normals. There was no tendency for either the R or M vector in the frontal plane to shift leftward with increasing pressure or gradient. The position of R in the horizontal plane ($\angle R_{hp}$) did correlate with gradient but at low confidence limits (Fig. 2).

Though there was no linear correlation, the position of the S vector in the horizontal plane ($\angle S_{hp}$) tended to be more leftward than in normals, and in the more severe cases approached the posteriorly rotated R vector, narrowing the angle between them ($\angle RS_{hp}$). Four patients had no S vector; each had an LVP above 210 mm. Hg.

There were no significant correlations between hemodynamics and the voltage of the Q vector. Its position ($\angle Q_{hp}$), however, was related to gradient. Q tended to be more toward the left or to disappear entirely as gradient increased. There was wider scatter of both voltage and direction of the Q than in a normal population. Except for one patient (No. 5) either an absent Q vector (No. 19) no identifiable Q

Table I. *Listing of patients with important individual measurements*

Patient			Press (mm. Hg)		QRS (msec.)	VCG voltage (mv.)						VCG angles (degrees)					ECG (mv or degrees)		
No.	Age	Sex	LV	VG		M_f	Q	R_h	S	M	R_hS	Q_{hr}	R_h	S	20	R S	R S V	S_V	∠QRS
1	37	F	134	—	100	1.62	0.20	1.12	0.92	1.65	1.33	115	352	265	335	87	1.0	1.7	61
2	15	M	150	18	96	2.07	0.92	2.18	1.06	2.18	1.15	128	024	283	24	101	0.6	1.3	6
3	52	M	170	73	96	2.42	0.14	2.48	2.08	2.48	1.08	130	355	242	28	113	1.0	1.4	10
4	13	M	174	60	100	2.70	0.28	2.70	1.05	2.70	1.35	135	000	235	0	125	0.7	1.6	25
5	20	M	182	—	100	2.12	—	2.19	0.75	2.18	1.18	—	347	260	226	87	0.5	1.6	17
6	6	M	182	90	80	2.75	0.35	2.80	1.50	2.80	2.20	99	351	283	32	68	1.5	2.3	52
7	18	M	182	94	116	2.30	0.46	2.22	1.01	2.37	1.40	96	334	247	43	87	1.3	2.4	40
8	47	F	190	118	96	2.69	0.10	2.90	1.88	2.90	1.35	90	329	295	66	34	1.2	2.3	40
9	53	M	194	76	92	2.51	0.20	2.66	1.40	2.66	1.40	175	343	275	18	68	1.0	1.9	40
10	43	F	200	70	96	2.20	0.12	2.44	0.95	2.44	0.80	180	020	355	122	25	0.5	2.2	−9
11	37	M	201	60	92	2.70	0.18	2.73	0.32	2.73	1.97	106	357	188	20	169	1.7	1.5	75
12	11	M	201	88	72	2.86	0.70	2.50	2.02	2.90	2.78	52	357	261	50	96	2.2	3.6	80
13	53	M	204	100	84	2.87	0.40	3.00	1.50	3.00	1.58	112	343	287	20	56	1.1	2.4	39
14	8	M	205	118	72	2.18	0.08	2.22	0.98	2.22	1.67	140	350	270	35	80	1.0	1.7	53
15	57	F	206	54	88	2.21	0.06	2.27	1.13	2.27	0.56	140	357	313	25	44	0.4	1.2	−18
16	41	M	210	80	116	2.40	0.22	2.58	—	2.58	1.37	—	335	—	21	—	1.4	2.4	−60
17	70	M	216	108	100	2.70	0.15	2.80	1.80	2.80	1.45	153	005	310	20	55	0.9	2.2	9
18	43	F	224	120	64	2.70	0.36	2.83	—	2.83	2.05	70	333	—	41	—	1.7	3.6	60
19	38	F	240	110	72	2.95	—	2.95	—	2.95	1.80	—	336	—	112	—	1.0	2.1	42
20	13	F	240	152	80	4.30	0.22	4.22	4.65	4.65	3.70	75	345	290	67	55	2.7	2.8	60
21	43	F	242	150	80	2.30	0.05	2.67	—	2.67	1.77	—	320	—	107	—	1.1	2.8	35
22	29	M	290	180	72	3.40	0.18	3.30	2.12	3.42	3.15	40	003	302	52	61	2.9	2.8	70
Mean	34		202	96	89	2.59	0.24	2.63	1.24	2.70	1.69	113	350	276	34	64	1.3	2.2	33
SD	18		33	38	14	0.54	0.22	0.56	1.03	0.57	0.74	39	16	36	52	44	0.7	0.7	34
Normal M					91	1.70	0.22	1.70	0.60	1.73	1.30	108	0	254	24	100			
SD					13	0.40	0.13	0.50	0.29	0.46	0.50	26	16	24	37	18			

Table II. Correlation coefficients of ventricular pressure (LVP) and valve gradient (VG) with VCG and ECG measurements

	Time QRS	VCG voltage				VCG angles				ECG		
		M_t	M	R	R, S	Q_{hp}	20_{sp}	R_{hp}	R–S	S_{V1}	R, S_{V_F}	SUM
LVP	−0.53	0.65	0.66	0.70	0.59	0	0.47	0	−0.48	0.54	0.59	0.63
VG	−0.52	0.59	0.63	0.64	0.66	−0.51	0	−0.49	−0.44	0.63	0.65	0.72

When n = 22 (LVP) $r_{.05}$ = 0.41, $r_{.01}$ = 0.53, $r_{.001}$ = 0.64.
When n = 20 (VG) $r_{.05}$ = 0.43, $r_{.01}$ = 0.55, $r_{.001}$ = 0.67.

in the hp (Nos. 16 and 21) or a Q vector directed to the left (Nos. 12, 18, 20, and 22) was associated with a LVP greater than 200 mm. Hg. Patients with no identifiable Q in the hp were also without a discernible S vector, again excluding Case 5. Those with neither Q nor S vector had pressures greater than 240 mm. Hg. Further evidence of abnormal initial forces appears in the correlation between the direction of the 20 msec. vector in the sagittal plane ($\angle 20_{sp}$) and LVP. This vector tends to become more inferoposterior with increasing gradient (Fig. 3).

An unexpected finding was the tendency for duration of the QRS loop to be less with the higher pressures (Fig. 3).

ECG. Voltage changes in Leads aV_F and V_1 correlated about as well as VCG measurements and their sum better than either alone (Fig. 4). This was, however, not true for R_{V5-6} and correlations were lower when this measurement was incorporated into voltage sums.

Left axis deviation (LAD) is an established criterion for LVH in adults, but only 3 cases had a mean QRS axis of less than zero. On the contrary, there was a tendency toward a vertical electrical position in the severe cases (Fig. 4).

Discussion

Various VCG configurations have been described in LVH. Their significance can be appreciated by noting the progressive changes which correlate with increasing pressure load. The R vector lengthens and may be displaced posteriorly. The S vector moves leftward and closer to R so that in severe cases it cannot be identified. Thus the somewhat triangular configuration of the normal horizontal plane loop gradually assumes an elongated elliptical appearance. Minor shifts in anterior-posterior relationship of afferent and efferent limbs may then cause a figure-of-eight or even a narrow clockwise rotation in the horizontal plane, the Type II and III loops described by others.[10,11] Such loops reportedly have the highest R voltages as well as highest pressure and gradients. Linear correlation, however, between voltage and position of vector R_{hp} is poor.

Many have speculated that the figure-of-eight or clockwise loop is due to incomplete left bundle branch block because of the slowing in its midportion and frequent association of a leftward Q vector.[10,1] This configuration, however, is apparently less common with the Helm system (one example in this series), possibly because it does not accentuate the posterior component of the Z lead as much as does the Frank system.[9]

Less specific conduction disturbances, even without prolongation of the QRS complex, can apparently increase voltage independently of ventricular mass.[12] Such blocks may be more common in older patients than is readily apparent and explain why voltages do not correlate as well with LVP in adults with AS as they do with pure right ventricular pressure loads of congenital origin.[13] Another possibility is the nonlinear hypertrophic response of the left ventricle to increasing loads as has been suggested in aortic insufficiency.[14]

Text continued on p. 43.

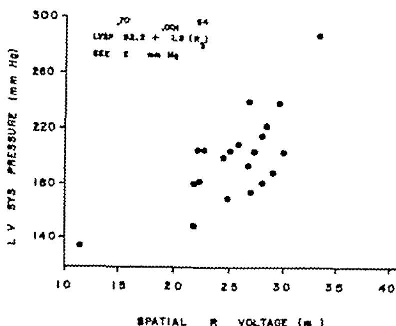


Fig. 2A. Two of the most important variables in the VCG which change with degree of pressure overload in aortic stenosis are shown here and in Fig. 2B. Spatial voltage of R usually increases with increased left ventricular pressure.

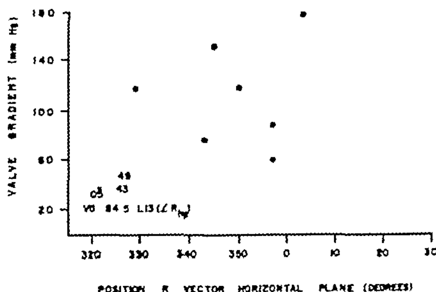


Fig. 2B. There is a similar tendency for R to shift posteriorly with increased load. The coefficient of correlation with pressure is just below the 5 per cent level.

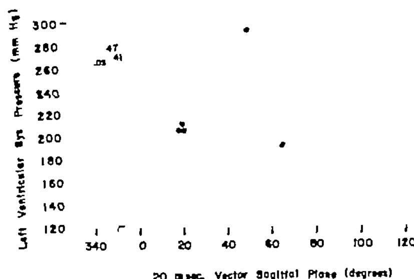


Fig. 3A Illustrates tendency for the 20 msec. vector to shift posteriorly with increasing pressure. Observations Case 5 are not plotted since they will not fit the scale. Note that in 4 patients (including Case 5), the 20 msec. vector was posterior (> 90 degrees) although none had clinical evidence of myocardial infarction (2 with normal coronary arteriograms).

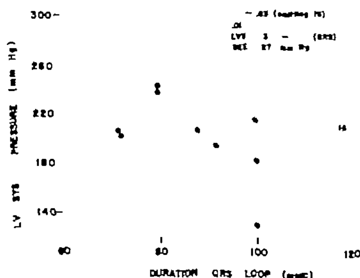


Fig. 3B A rough inverse correlation exists between QRS duration and the pressure load. Case 16 (axis −60 degrees, QRS duration 116 msec.) probably has a form of intraventricular block, and was therefore omitted from the calculation of

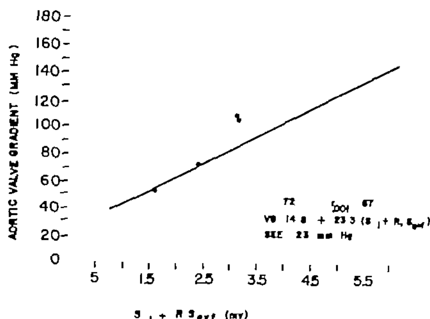


Fig 4 1 The best correlation between pressure or gradient and several ECG indices of LVH tested is illustrated here It is as good as any for the VCG measurements.

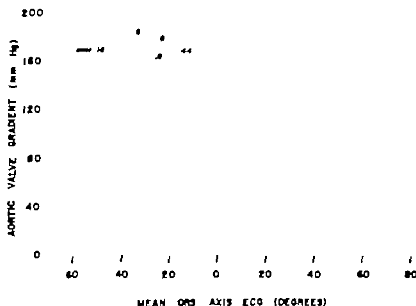


Fig 4B Mean QRS axis ppears to be partially a function of pressure gradient with the more vertical axes being associated with the higher pres ures. The relationship probably does not hold, however if patient with marked left axis deviation representing intraventricular block are included. Case 16 (axis −60 degrees, QRS duration 116 msec.) is identified.

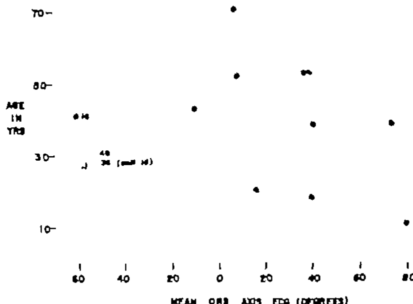


Fig. 5A. Two further independent influences on mean QRS axis in aortic stenosis are shown here and in Fig. 5B. The normal trend toward left axis with increasing age can be detected in spite of wide variations in severity of the overload. The statistical significance is low, however, even if Case 16 is not included.

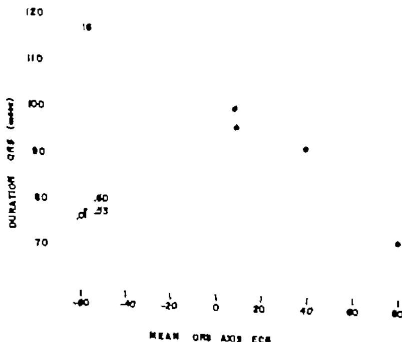


Fig. 5B. Evidence suggesting an association between horizontal or left axis and slight delay in completion of left ventricular depolarization.

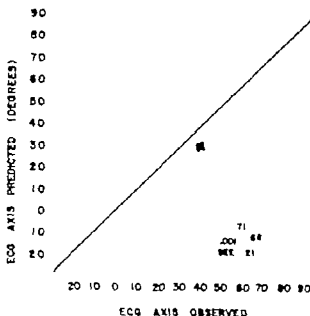


Fig. 6A. Correlation between predicted and observed ECG axis. The prediction equation employs the 3 variables which correlat with axis valve gradient, age, and QRS duration. It is as follows axis = 77.8.88 + 0.26114 (VG) − 0.5738 (age) − 0.5578 (QRS). The predictions for those cases with n axis higher tha 0 degrees (including Case 16 not plotted) vary more than the standard error of the estimate. The addition of "QRS" only increases r from 0.68 to 0.71

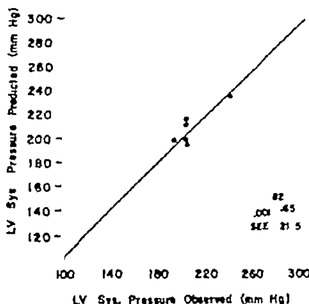


Fig. 6B. Correlation between measured left ventricular pressure nd that predicted by a m ltiple regression equation utilizing the spatial voltage of vector R the duration of the QRS loop (msec.) and the angle of the Q vector in the horizontal plane (degrees). LVP = 209.596 + 30.828 (R) − 0.871 (QRS) − 0.27 (∠Q). The tandard error of this estimate was slightly lower than th t for a similar equation for predicting valve gradient Coefficient of correlation could be gradually increased to a maximum of 0.86 by the addition of 4 more variables. The resulting equation however was considered impractical because of its complexity and failure to decrease the error of estimate.

Case 16 was omitted in the calculations but, nevertheless its prediction wa within the stand rd error

The Q vector was found to be frequently abnormal and directed to the left by Wallace and co-workers.[9] Conceivably this could be due to one or more of the following: a change in orientation of the plane of the septum with LVH, septal scarring, or incomplete left bundle branch block. The wide scatter and weak correlation of Q voltages and directions suggest that changes in Q may vary independently of the remainder of the loop. This is supported by the absence of correlation between voltages or angles of R and those of Q.

The tendency for the duration of QRS to be less with higher pressure is curious and may represent a fundamental difference in conduction velocity through dilated and concentrically hypertrophied hearts. Positive correlations of QRS time with ventricular size appear to exist in the higher normal values of adults as compared to children, in the dilated hearts of cardiomyopathy,[18] and in volume overloading of atrial septal defect and aortic insufficiency.[1, 17] In contrast, even severe pressure loading of the right ventricle ordinarily does not increase QRS duration.[19]

There was significant correlation between hemodynamic findings and voltage of the maximum vector of the frontal plane (always either the R vector or one very close to it) and with the amplitude of the projection of this vector on the Y axis (R, R_a). This is probably the result of one or more of the following factors: (1) the infrequency of LAD, (2) the vertical lead may be less affected by variation in dipole location, body build, etc. than Leads X and Z, and (3) the augmented voltage associated with concentric hypertrophy may be directed mostly inferiorly. Therefore voltage of Lead aV_F appears to deserve greater emphasis as an index of LVH in patients with pressure overloading. In those without LAD it may be of more value than the more widely used precordial lead criteria, particularly $R_{V5, 6}$, which in this study showed no significant correlations.

Since a vertical electrical axis is more common in younger patients (Fig. 5A) it seemed possible that the predictive value of aV_F or other voltages might exist mainly because most of the patients were young. If they are subdivided at age 40 into 2 groups, the severity of disease is comparable since LVP does not differ significantly (over 40 = 206 ± 20, under 40 = 199 ± 42). The mean voltages are also similar. Coefficients of correlation, however, between LVP and voltages of aV_F, R_Y, M_Y, and M_{fp} are not significant ($p > 0.10$) for the older patients but are for the younger ones ($p < 0.01$). It seems clear, therefore, that the validity of predictive equations employing these measurements does depend largely upon the younger patients and would be least reliable in older adults.

The association of vertical axis with pressure overloading of the left ventricle has been previously noted.[17] In this study, however, axis also appears to be a function of age independent of pressure, as it is in normals (Fig. 5). There is also a tendency for the ECG's with the more leftward axes to have higher values for QRS duration. This supports the suspicion that some of these may represent subtle forms of intraventricular block (Fig. 5). If these independent factors associated with the axis of the ECG are suitably combined in a multiple regression equation, the prediction of axis for a given case is statistically highly significant (Fig. 6). It is surprisingly good considering the wide scatter of axes encountered in the normal population.

The sponge VCG was found to provide easily measurable parameters that correlate reasonably well with the hemodynamic findings in patients with fixed left ventricular outflow obstruction. Two laboratories have reported previously on this problem in children and young adults, utilizing the Frank VCG.[4, 15] The results varied widely and inexplicably. The present study yields coefficients of correlation which are intermediate between their results. Equations generated by stepwise multiple regression utilizing several variables considerably improves the value of the ECG and VCG for predicting pressure and gradient (Fig. 6). The independent variables tested were duration of QRS, $\angle Q_{max}$, $\angle R_{max}$, $\angle 20_{ms}$, $\angle QRS_{ECG}$, and voltages R_Y, Sum S_{V_1} + R_{V_5}.

Summary

Twenty-two patients, with a mean age of 34 years (range 6 to 70) and chronic left ventricular outflow obstruction were studied by left heart catheterization, sponge

VCG and standard ECG The best correlations of hemodynamic and electrical data were between either left ventricular pressure or gradient across the obstruction and spatial R or maximum vector voltages. Lesser but significant correlations were found with a shift of the early vectors (Q and 20 msec.) toward the left inferior and posterior and R posteriorly Significant correlations were also found with voltages from the ECG (S_{V_1} R $_{V_5}$, and their sum) Excluding a patient with severe LAD the *mean QRS axis in the ECG tended to shift* vertically with increasing pressure load. In addition axis appears related to age and the duration of the QRS complex.

The value of single measurements from the VCG or ECG in predicting LVP or gradient is limited but estimates can be improved by combining several into a multiple regression equation. Reliability is expected to be less in older adults. In addition a VCG pattern for patients with LVP's above 210 mm. Hg is noted This consists of an increased spatial R vector plus either a leftward or absent Q vector in the horizontal plane, an absent S vector or both.

REFERENCES

1. Braunwald, E., Goldblatt, A., Aygen, M D Rockoff S. D and Morrow A. G. Congenital aortic stenosis I Clinical and hemodynamic findings in 100 patients, Circulation 27:426, 1963.
2. Hancock, E. W and Fleming, P R. Aortic stenosis, Quart. J Med. 29:209 1960.
3. Baronofsky I D Steinfeld, L., Kreel, I Gordon, A. O and Grishman, A. Congenital aortic stenosis Diagnosis and surgical treatment, New York State J Med. 59:4349 1959
4. Hugenholtz, P G., and Gamboa, R. Effect of chronically increased ventricular pressure on the electrical forces of the heart, Circulation 30:511 1964.
5. Baker C., and Sommerville, J Critical congenital aortic stenosis with minimal electrocardiographic changes, New England J Med. 262:276 1960.
6. Helm, R. A.: An accurate lead system for spatial vectorcardiography Am. Heart J 53:415, 1957
7. Witham, A. C. Quantitation of the vectorcardiogram, Am. Heart J 72:284 1966.
8. Witham, A. C.: The vectorcardiogram recorded with sponge electrodes, Am. Heart J 72:730, 1966.
9. Helm, R. A. Vectorcardiographic notation, Circulation 13:581 1956.
10. Wallace, A. G., McCall, B W., and Estes, E. H: The vectorcardiogram I left ventricular hypertrophy Am. Heart J 63:466 1962.
11. Varriale, P Alfenito, J C. and Kennedy R. G The vectorcardiogram of left ventricular hypertrophy Analysis and criteria, Circulation 33:569 1966.
12. Watt, T B Jr Murao, S., and Pruitt, R. D.. Left axis deviation induced experimentally in a primate heart, Am. Heart J 70:381 1965.
13. Witham A. C. Rainey R. L., and Edmonds, J H J Prediction of right ventricular pressure in pulmonic stenosis from sponge vectorcardiogram and electrocardiogram, Am. Heart J 75 187 1968.
14. Rainey R. L., Besseghini, L, Witham, A. C., and Edmonds, J H., Jr Relationships between mass, volume, and voltage I aortic insufficiency Circulation (II) 36:215 1967 (abstr).
15. Brigden, W: Uncommon myocardial diseases. The non-coronary cardiomyopathies, Lancet 2 1179 1957
16. Edmonds, J H Witham, A. C., Rainey R. L., and Harden, T P: Correlation between hemodynamics and quantitated QRS vectors in atrial septal defect, to be published.
17. Sodi-Pallares, D and Calder R. M.. New bases of electrocardiography St. Louis, 1956, The C. V Mosby Company p. 247
18. Reeve, R., Kawamata, K., and Selzer A.: Reliability of vectorcardiography in assessing severity of congenital aortic stenosis, Circulation 34:92, 1966.

Experimental and laboratory reports

Natural history of experimental coronary occlusion in pigs: A serial cineangiographic study

Yihong Kong, M.D.
James T. T. Chen, M.D.
Howard J. Zeft, M.D.
Robert E. Whalen, M.D.
Henry D. McIntosh, M.D.
Durham, N. C.

Despite many excellent studies of the coronary circulation little is known about the serial changes of the coronary arteries and the development of collateral circulation during the course of a gradual coronary occlusion. Although the development of the coronary collaterals has been studied by postmortem coronary arteriography,[1-11] it has not been evaluated by serial observations in vivo. In order to study these processes in a living animal serial selective coronary cineangiograms were done in a group of farm pigs after placement of an Ameroid constrictor on the left anterior descending artery. The findings of these studies constitute the following report.

Methods

A total of 32 farm pigs, weighing 25 to 35 pounds were studied. Gradual coronary occlusion was produced by surgical placement of an Ameroid constrictor on the left anterior descending artery as described by Litvak and associates.[12] With halothane† anesthesia, the heart of the animal was exposed through a left thoracotomy. An 8 to 10 mm. segment of the left anterior descending coronary artery beginning at its origin was then freed by blunt dissection and an Ameroid constrictor with a central lumen of 1.5 mm. diameter was placed around the exposed segment. The Ameroid constrictor did not interrupt the blood flow initially but by its hygroscopic nature it gradually occluded the vessel by external compression. After placement of the constrictor the thoracotomy was closed by layers and the air from the pleural space was eliminated through a chest tube. The animals usually recovered from anesthesia promptly and were ambulatory within 3 hours after surgery. In order to prevent the serious ventricular arrhythmias associated

From the Cardiovascular Laboratory, Department of Medicine and Department of Radiology, Duke University Medical Center, Durham, N. C. 27706.
Presented at the 40th Scientific Sessions of the American Heart Association, San Francisco, Calif. Oct. 21, 1967.
Supported in part by Grant [illegible], HE-11307, HE-5736, and HE-4807 from the National Heart Institute, United States Public Health Service, and grants-in-aid from the North Carolina and American Heart Associations and The John A. Hartford Foundation, Inc.
Received for publication Dec. 22, 1967.
*Work completed during tenure of Vocational Rehabilitation Administration Fellowship.
†Kindly supplied by Dr. John R. Jewell, Ayerst Laboratories, New York, N. Y.

with myocardial ischemia antiarrhythmic drugs were given through an indwelling venous catheter in the first 3 postoperative days. Each animal received either quinidine gluconate 5 mg per kilogram every 6 hours or diphenylhydantoin (Dilantin) 20 mg per kilogram initially and then 5 mg per kilogram every 8 hours.

After placement of the constrictor both left and right coronary arteries were evaluated by serial selective coronary cineangiograms at various intervals until the death of the animal. These studies were carried out under light anesthesia with pentobarbital and controlled respiration with a Harvard respirator. A Sones catheter was inserted into the aorta through a cut-down on the carotid artery and was manipulated into the ostium of either coronary artery. Cineangiograms of various projections were then obtained during the hand injections of 5 to 6 ml. of sodium and N methyl glucamine metrizoate (Isopaque-440).† These cineangiograms were taken at a speed of 60 frames per second with a 5 inch image intensification system and 35 mm Kodak double X cine films. The resolution of the cinefluorographic system has been actually tested in these animals and found to be capable of demonstrating vessels as small as 300 μ.

The original 35 mm. cineangiograms were reduced on 16 mm films and analyzed with a Kodak Analyst" movie projector. Two projectors were used simultaneously for analyzing films obtained from the same animal on different days. During the analysis the caliber of various vessels was measured and the speed of the filling and clearance of contrast medium was determined. In order to eliminate the differences of magnification the diameter or the width of the metal ring of the constrictor was used as the reference standard for the measurement of size and distance. The time required for filling or clearance of contrast medium in the constricted anterior descending artery was compared with that of the circumflex branch and the difference in time was crudely estimated in terms of numbers of frames. Collateral circulation in each animal was graded as follows: *Grade I*, minimal collateral circulation with opacification of less than ⅓ of the main anterior descending artery and none of its branches; *Grade II*, opacification of ⅓ to ⅔ of the main anterior descending artery and some of its major branches; *Grade III*, opacification of more than ⅔ of the anterior descending artery and all of its major branches; and *Grade IV*, demonstrable increase of size and number of collateral channels with opacification of the whole anterior descending artery including its major and secondary branches.

Detailed pathological examinations of the hearts were carried out after the death of the animals. The areas of myocardial infarction were first carefully mapped during the gross examination. Multiple sections from both ventricles and the interventricular septum were then obtained for the hematoxylin-eosin stains and microscopic examinations. The pathological findings were graded with the following scale: *Grade O*, no pathological findings; *Grade I*, minimal spotty necrosis in the subendocardium; *Grade II*, scattered areas of subendocardial infarction; *Grade III*, uniform subendocardial infarction; and *Grade IV*, large transmural infarction.

The rate of closure of the Ameroid constrictor was also studied in vitro by incubating 2 Ameroid constrictors in physiological saline at 37° C. Close up photographs of these Ameroid constrictors taken with background illumination and identical photographic techniques were obtained before and at 6-hour intervals after the beginning of incubation. All photographs were enlarged to the size of 5 × 7 inches. The areas of both central lumen and the whole constrictor were measured with a compensating polar planimeter. The change of the area of the central lumen at various intervals was then calculated with reference to the constant total area of the constrictor. By assuming the cross-section of the central lumen as a perfect circle the corresponding changes in diameter were also derived.

Results

Fifty-seven coronary cineangiographic studies were carried out in 32 pigs. Fifteen pigs were studied once, 11 pigs twice, 4 pigs

Kindly supplied by Dr. A. C. Bratton, Jr., Parke, Davis, and Company, Detroit, Mich.

†Kindly supplied by Dr. Franklin F. Teller, Winthrop Laboratory, New York, N. Y.

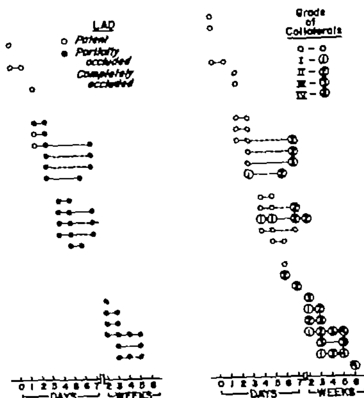


Fig 1 Time-course of coronary occlusion (left panel) and the development of collateral circulation (right panel). The time after the placement of the Ameroid constrictor is indicated on the bottom. Each circle represents coronary cineangiographic study Circles connected by broken line represent serial studies on the same animals. The degrees of the occlusion and the magnitudes of collateral circulation are indicated by symbols shown at the right upper corner of each panel.

3 times, and 2 pigs 4 times. The time interval between the study and placement of the constrictor are shown in Fig 1 Five or more animals were studied during each of the first 7 days (except the first postoperative day) and during the second and third week after the placement of the constrictor Only 2 3 and 1 animals were studied in the fourth, fifth and sixth week, respectively

Time course of coronary occlusion. No appreciable stenosis of left anterior descending artery was observed in the first 48 hours after placement of the constrictor Delay in filling and clearance of contrast medium was apparent in studies obtained from 48 to 72 hours. By the third day appreciable narrowing of the anterior descending artery began to appear at the areas just proximal and distal to the Ameroid constrictor Poststenotic dilatation was frequently seen. The time of complete occlusion varied from 3 to 11 days but in the majority of animals it occurred between the sixth and seventh day (Figs. 1 and 2)

Time course of development of collateral circulations Collateral circulation was not demonstrated until the sixth or seventh day in most of the animals. It usually appeared only after the anterior descending artery was completely occluded. These collateral channels gradually increased in size and number in the subsequent 2 to 3 weeks, and by the fifth to the sixth week the main collateral vessel approached almost the same caliber of that of the anterior descending artery (Figs. 1 and 3)

Magnitude of collateral circulation The magnitude of collateral circulation varied from animal to animal (Fig 1) In general it was only Grade I to II in the first 2 weeks and increased to Grade II to III in the third and fourth week. By the fifth or sixth

week it further increased to Grade IV and the circulation in the left anterior descending artery was completely re-established through the collateral channels.

Types of collateral channels The types of collateral channels are shown in Table I and Fig 4 In 16 animals, which survived longer than six days, collateral channels were seen in 15 Homocoronary collateral vessels from the proximal segment of the left anterior descending artery were demonstrated in 8 animals. In 11 animals, there were intercoronary collateral channels from the left circumflex artery mainly from the marginal and muscular branches. Intercoronary collateral channels from the right coronary artery were seen in 13 pigs. The major communications usually occurred between the posterior descending branch and anterior descending artery

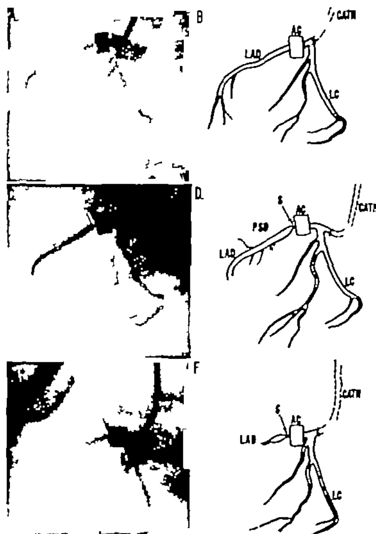


Fig 2 Serial changes of the left anterior descending artery after placement of the Ameroid constrictor
(*A*) and (*B*). A cine frame and the corresponding line drawing of the left coronary arteriogram taken on the second day Note the normal filling and caliber of the left anterior descending artery *AC* Ameroid constrictor *CATH* Catheter *LAD* left anterior descending artery and *LC*, left circumflex artery
(*C*) and (*D*). The coronary arteriogram of the same animal obtained on the third day shows the severe stenosis (arrow *S*) and poststenotic dilatation (*PSD*) distal to the constrictor
(*E*) and (*F*) Coronary arteriogram of the same pig taken on the seventh day The occlusion was almost complete. Only a very short segment of the left anterior descending artery was filled.

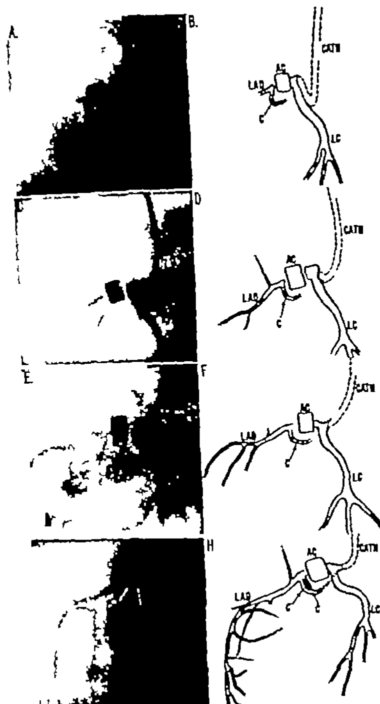


Fig. 3. Serial studies on one animal showing the development of collateral circulation after placement of the Ameroid constrictor.
(*A*) and (*B*), The coronary arteriogram obtained on the tenth day shows the complete occlusion of the left anterior descending artery (LAD) and Grade I collateral circulation. The left anterior descending artery was filled by collateral channel (arrow *C*) arising proximal to the constrictor. Less than a third of the left anterior descending artery was filled and none of its branches was opacified.
(*C*) and (*D*) An arteriogram obtained on the seventeenth day demonstrates the increase of collateral circulation to Grade II. More than a third of the left anterior descending artery was filled and some of its major branches were opacified.
(*E*) and (*F*), An arteriogram obtained on the twenty-fifth day demonstrates Grade III collateral circulation. Two thirds of the left anterior descending artery and most of the major branches were filled.
(*G*) and (*H*), An arteriogram taken on the thirty-first day demonstrates Grade IV collateral circulation. Note the increase of size and number of the collateral channels. The whole length of the left anterior descending artery was filled, also its major branches and some of the secondary branches.

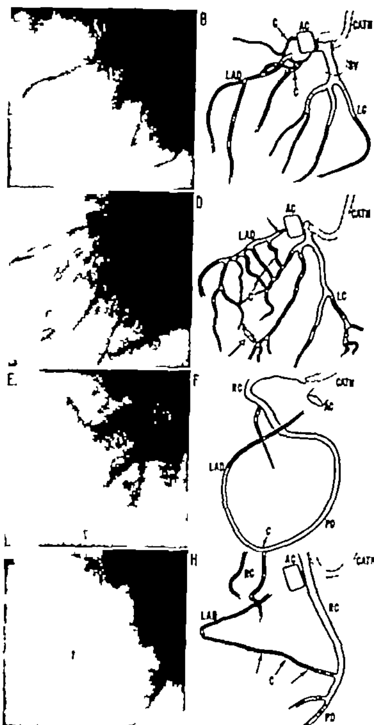


Fig. 4 Patterns of collateral circulation. (A) and (B) Multiple collateral channels developed from the left anterior descending artery proximal to the Ameroid constrictor. AC Ameroid constrictor; C, collaterals; CATH catheter; LAD left anterior descending artery; LC left circumflex artery; SV sinus Valsalva.
(C) and (D), Multiple collateral channel (small arrows) developed from m scula branch and marginal branch of left circumflex artery. Myocardial blush can also be seen (large arrow).
(E) and (F) An arteriogram show the retrograde filling of the left anterior descending artery through the collateral channel (arrow) from posterior descending artery (PD) of the right coronary artery (RC).
(G) and (H). The left anterior descending artery was filled by septal branch (arrow) of the right coronary artery

around the apex between the anterior and posterior septal branches through the ventricular septum and between the conal branches of both coronary arteries around the pulmonary artery

Pathological studies Areas of myocardial infarction with Grade III to VI changes were found in all animals which survived longer than 2 days. These changes were present regardless whether the left anterior descending artery was completely or only partially occluded at the time of death. The development of collateral circulation did not prevent the myocardial infarction or decrease the severity of myocardial necrosis in these animals.

The rate of closure of the Ameroid constrictor in saline at 37° C. is shown in Fig 5 In the first 2 days, the rate of constriction was relatively fast. The central lumen was reduced to 68 and 58 per cent of the original area at 24 and 48 hours, respectively The progression of the narrowing became very slow after 60 hours, with the area of the central opening remaining 48 per cent of the original size at the end of one week and 36 per cent at the end of 2 weeks. The per cent change in diameter of the central lumen was much less than that of the area. It only reduced to 83 and 77 per cent of the original measurement at 24 and 48 hours respectively to 69 per cent at the

*Table I Types of collateral circulation**

Type	*No. of Pigs*
Homocoronary	8
Intercoronary	
From left circumflex artery	11
Muscular branch	7
Marginal branch	8
From right coronary artery	13
Conal branch	4
Septal branch	3
Posterior descending branch	10

*Findings in 16 pigs that survived longer than 4 days after placement of an Ameroid constrictor

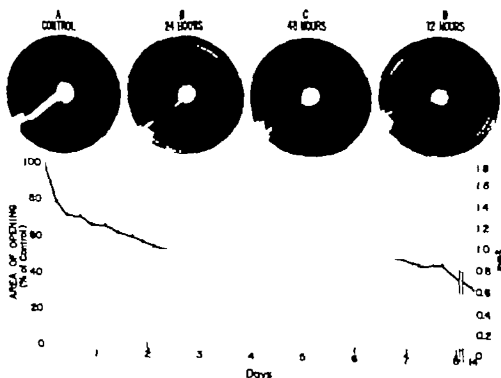


Fig. 5 Rate of closure of the Ameroid constrictor incubated at 37° C. Upper: photographs of the same Ameroid constrictor taken before (*A*) and after incubated for 24 hours, (*B*) 48 hours, (*C*) and 72 hours (*D*). Lower: curve showing the change of central opening of the Ameroid constrictor incubated in normal saline at 37° C.

end of one week and to 60 per cent at the end of 2 weeks.

Discussion

Despite many excellent studies of the coronary circulation little is known about the serial change of the coronary arteries and the development of collateral circulation during the course of a gradual coronary occlusion Although coronary arteriograms have been fortuitously done in patients either before or after the occurrence of an acute myocardial infarction serial observations are not available. In animal studies, the findings have been varied with the species of animal used and the methods of studies employed [8,10,13 6]

Many of the previous studies were carried out in dogs. [8 4,14] The canine coronary arterial system is quite different from that of man.[17 20] First the right coronary artery of the dog is small the posterior surface of *the heart is almost always supplied by the* left circumflex artery This pattern of coronary circulation is only found in 10 per cent of human hearts.[1] Second the interventricular septum of dogs is supplied almost exclusively by a large single septal branch of the left anterior descending artery [18,19] whereas, in man it is supplied by 4 to 6 branches from the anterior descending artery [17] Finally pre-existing interarterial communication with a diameter larger than 100 μ are frequently demonstrated [1 13,18,19] Such large functioning interarterial communications have not been demonstrated in normal man

In the present study farm pigs were used because of the similarity of the coronary distribution to that of man[4,20,21] and the absence of significant pre-existing collateral channels.[1 4,20 21] It has been demonstrated that intercoronary anastomosis only exists in less than 2 per cent of the animals.[21] It is usually of minimal degree and located at the apex between the right coronary and the left anterior descending arteries Coronary arteriograms were performed in 2 animals in the present series during acute *temporary* occlusion of the anterior descending artery with a plastic snare no pre-existing collateral channels could be demonstrated either from the right coronary or from the left circumflex artery

In most of the previous studies the coronary circulation was evaluated mainly with postmortem coronary arteriograms after perfusion of radiopaque particles. With this technique the coronary circulation cannot be studied in a living state, the dynamic nature of the collateral circulation cannot be evaluated the temporal relationship of the arterial narrowing and the development of collateral circulation is difficult to determine finally serial observations cannot be made in the same animals. The demonstration of the patency of the constricted vessel and the extent of collateral circulation also *varies greatly with the size of particles used* in the perfusion mass. These particles are usually much larger than the blood cells and with a viscosity much higher than the blood

Most of these problems were obviated in the present study since coronary cineangiograms were done serially in living animals. Furthermore the injected contrast *medium was mixed and circulated* with blood so that the appearance and subsequent clearance of contrast medium in the collateral channels not only demonstrated the anatomical presence of these vessels, but also indicated their active physiological function Although vessels smaller than 300 μ in diameter might not be well demonstrated by cineangiography as individual vessels their presence was frequently indicated by the appearance of a myocardial blush

In previous studies utilizing postmortem injection techniques, Ameroid constrictors of the size used in this study were believed to occlude the coronary artery completely within 36 to 48 hours after the placement.[1-3] However this has not been demonstrated in vivo The data from the present study indicates that the closure of the central lumen of the constrictor is much slower In vitro the closure was still incomplete even after 2 weeks incubation in saline. In vivo complete occlusion of the left anterior descending artery did not occur until the sixth or seventh day after placement of the constrictor In our experience the rate of closure has been found to be quite consistent in the constrictors from the same lot. However slight variations between batches have also been observed. This variation may explain part of the discrepancy in the findings observed in the

present and the previous studies. It is also important to note that despite the slow closure of the constrictor demonstrated by cineangiograms, extensive myocardial infarction was found in all animals surviving longer than 2 days. This finding indicates that in this preparation significant myocardial ischemia had occurred long before the complete occlusion of the coronary artery and the development of demonstrable collateral channels.

In the present study collateral vessels were demonstrated 6 to 7 days after the placement of the constrictor and only after the coronary artery was significantly narrow or completely occluded. Although the magnitude and extent of the collateral circulation gradually increased within 2 to 3 weeks, 5 to 6 weeks was often necessary to completely re-establish the circulation in the constricted vessel. These findings correspond to those of Lumb and Hardy[3] who with a postmortem injection technique, could only find collateral channels in pigs surviving longer than 4 days after placement of the Ameroid constrictor. However Paul and co-workers[12] found that anastomoses could be demonstrated in pigs 2 days after acute occlusion of a coronary artery. Blumgart and colleagues[4] showed in post mortem injection studies that if the arterial lumen was acutely narrowed to less than 25 per cent of the original size, collateral circulation appeared within days, however 12 or more days were generally necessary for evolution of a rich anastomosis. Eckstein and associates[14] utilizing the retrograde flow method in dogs, demonstrated that the retrograde flow shortly after ligation of the left anterior descending artery was very small, ranging from 0.5 to 5.8 c.c. per minute. It increased very slowly and did not attain a sizable value until 2 to 6 days after the occlusion.

At present, there is no satisfactory method to determine whether these collateral channels are pre-existing or form de novo after the coronary occlusion. Using postmortem injection technique, Paul and co-workers[12] demonstrated that pre-existing intercoronary anastomoses was very rare in normal young pigs, and was only found in 3 of the 161 animals studied. However the injection technique and perfusion mass used in the study only allowed filling of vessels larger than 50 μ. The incidence and distribution of the collateral channels of smaller size are still unknown. In the present study collateral filling of the left anterior descending artery was not found in any animals studied within 48 hours after placement of the Ameroid constrictor. In 2 additional animals, contrast medium was selectively injected into the right coronary artery and the left circumflex artery during an acute temporary occlusion of the left anterior descending artery, no collateral channels or filling of the occluded artery could be demonstrated. These observations would suggest that either the anastomotic channels are not present before the coronary occlusion or if present they are not physiologically functioning. The time interval between the occurrence of significant coronary narrowing and the appearance of collateral circulation is relatively short as demonstrated in the present and previous studies. It is quite possible that these collateral channels are pre-existing and are normally very small and they do not become enlarged or physiologically functioning until a differential pressure develops after the coronary occlusion.

There has been considerable interest in the functional significance of coronary collateral circulation and whether a myocardial infarction can be prevented by the development of these anastomoses. This study was not designed to evaluate the adequacy of the collateral circulation, however, the finding of an extensive myocardial infarction in all animals surviving longer than 2 days is important. It indicates that in this preparation significant myocardial ischemia had occurred before the appearance of demonstrable collateral channels and the rapidity and the extent of the subsequent collateral development were not adequate to modify the outcome of the coronary occlusion.

Although the coronary distribution in pigs is similar to that of humans, one still must be cautious in extrapolating these data to the clinical situation. There are basic differences in species, the process of coronary occlusion and the extent of pre-existing atherosclerotic lesions. However the pig with gradual occlusion of a coronary artery by an Ameroid constrictor is being used more and more as an experimental

model for a variety of studies of myocardial infarction. The base line information and the natural history obtained in the present study are essential for the interpretation of such investigations.

Summary

In order to evaluate in vivo, the serial changes of the coronary arteries and the development of collateral circulation during the course of a gradual coronary occlusion 32 farm pigs were studied with serial selective coronary cineangiograms following placement of an Ameroid constrictor on the left anterior descending coronary artery. Delayed clearance of contrast medium and poststenotic dilatation of the constricted artery appeared by the second to third day, complete occlusion on the sixth to seventh day. Demonstrable collateral vessels developed in most of the surviving animals by the sixth to seventh day. These channels increased in size and number in the subsequent 4 to 5 weeks so that the left anterior descending artery distal to the constrictor again became completely opacified through the collateral channels. In 16 animals that survived longer than 6 days, major collateral channels perfusing the distal portion of the obstructed artery arose proximal to the constrictor in 8, from the left circumflex artery in 11, and from the right coronary artery in 13. Despite the development of such collateral circulation, massive myocardial infarction developed indicating that the rapidity and/or extent of the collateralization was inadequate to prevent myocardial death. These findings also provide the basic information needed for using this preparation as the model for studies of myocardial infarction.

REFERENCES

1. Lamb, G., and Hardy, L. B.: Collaterals and coronary artery narrowing. I. The effect of coronary artery narrowing on collateral channels in swine. Lab. Invest. 13:1530, 1964.
2. Lumb, G., Singletary, H. P., and Hardy, L. B.: Collateral circulation following experimental gradual narrowing of the coronary arteries. Angiology 13:463, 1962.
3. Lumb, G., and Hardy, L. B.: Collateral circulation in the heart. North Carolina Med. J. 24:456, 1963.
4. Blumgart, H. L., Zoll, P. M., Freedberg, A. S., and Gilligan, D. R.: Experimental production of intercoronary arterial anastomoses and their functional significance, Circulation 1:10, 1950.
5. Lumb, G. D., and Hardy, L. B.: Collateral circulation and survival related to gradual occlusion of the right coronary artery in the pig. Circulation 27:717, 1963.
6. Donald, D. E., and Essex, H. E.: Studies on chronic effects of ligation of canine right coronary artery. Am. J. Physiol. 176:431, 1954.
7. Blum, L., Schauer, G., and Calef, B.: Gradual occlusion of coronary artery: experimental study. Am. Heart J. 16:159, 1938.
8. Burchell, H. B.: Adjustments in coronary circulation after experimental coronary occlusion, with particular reference to vascularization of pericardial adhesions, Arch. Int. Med. 65:240, 1940.
9. Schlesinger, M. J.: Injection plus dissection study of coronary artery occlusions and anastomoses, Am. Heart J. 15:528, 1938.
10. Zoll, P. M., and Norman, L. R.: Effects of vasomotor drugs and of anemia upon interarterial coronary anastomoses, Circulation 6:832, 1952.
11. Jones, A. M.: The functional role of intercoronary anastomoses, Acta Cardiol. Suppl. 11:130, 1965.
12. Litvak, J., Siderides, L. E., and Vineberg, A. M.: The experimental production of coronary artery insufficiency and occlusion, Am. Heart J. 53:518, 1957.
13. Paul, M. H., Norman, L. R., Zoll, P. M., and Blumgart, H. L.: Stimulation of interarterial coronary anastomosis by experimental acute coronary occlusion, Circulation 16:608, 1957.
14. Eckstein, R. W., Gregg, D. E., and Pritchard, W. H.: Magnitude and time of development of collateral circulation in occluded femoral carotid and coronary arteries, Am. J. Physiol. 132:351, 1941.
15. Gregg, D. E., Thornton, J. J., and Mautz, F. R.: Magnitude, adequacy and source of collateral blood flow and pressure in chronically occluded coronary arteries, Am. J. Physiol. 127:161, 1939.
16. Wiggers, C. J.: Inadequacy of normal collateral coronary circulation and the dynamic factors concerned in its development during slow coronary occlusion, Am. Heart J. 11:641, 1936.
17. James, T. N.: Anatomy of the coronary arteries, New York, 1961, Paul B. Hoeber, Inc.
18. Pianetto, M. B.: The coronary artery of the dog, Am. Heart J. 18:403, 1939.
19. Moore, R. A.: The coronary arteries of the dog, Am. Heart J. 5:743, 1930.
20. Lumb, G., and Singletary, H. P.: Blood supply to the atrioventricular node and bundle of His. A comparative study in pig, dog, and man, Am. J. Path. 41:65, 1962.
21. Lumb, G., and Singletary, H. P.: Blood supply to cardiac conductive tissue in pig and man, Surg. Forum 12:218, 1961.

Aortic pressure loading in dogs with myocardial infarction

William B Hood, Jr M.D
Brian McCarthy Ph.D
Bernard Lown M.D
Boston, Mass

Acute myocardial infarction in experimental animals does not usually result in chronic congestive heart failure. Extensive destruction of normal myocardium most often leads to death from arrhythmias or shock, or to recovery It is well recognized, however that overloading the left ventricle may reveal defects in ventricular function which are not apparent in the resting state. Accordingly the following study was carried out to determine whether pressure loading of the left ventricle could be used to distinguish between experimental animals with normal hearts and with myocardial infarction. In addition the response to the inotropic agents acetylstrophanthidin and isoproterenol during pressure loading was assessed

Methods

Mongrel dogs weighing 16.5 to 23.5 kilograms were anesthetized with 30 mg per kilogram of pentobarbital given intravenously and subjected to thoracotomy and two-stage ligation of the left anterior descending coronary artery The ligation was carried out approximately 2 cm. below the bifurcation of the left main coronary artery just below the first major branching vessels. Ten animals of the 22 which were operated upon, survived the period of ventricular arrhythmia which invariably followed this procedure. An additional 7 animals were subjected to a sham operation and serve as controls.

On the third or fourth day following thoracotomy when ventricular arrhythmias had disappeared animals were given 1.5 mg per kilogram of morphine sulfate intramuscularly then anesthetized with 0.3 c.c. per kilogram of a mixture containing 200 mg of urethane 50 mg of allobarbital and 30 mg of pentobarbital per cubic centimeter given intravenously Fifty milligrams of heparin was also administered intravenously Animals were ventilated with room air via an endotracheal tube using a Harvard respiratory pump

The animals were instrumented for measurement of pressures and cardiac output as follows catheters were inserted into the right atrium and aortic root for pressure measurement. Cardiac output was measured by the indicator dilution technique with injection of indocyanine

From the Cardiovascular Research Laboratories of the Department of Nutrition, Harvard School of Public Health, and Medical Clinics, Peter Bent Brigham Hospital, Boston, Mass.

Supported by grants-in-aid from the National Institutes of Health (HE-07776-04, 5 T1 HE-5242, and PO-1-HE-11306-01) the John A. Hartford Foundation; and the Fund for Research and Teaching, Harvard School of Public Health, Department of Nutrition.

Received for publication Dec. 26, 1967

green dye into the right atrium and sampling from a fiberoptic catheter placed in the arch of the aorta using methods previously described.[3] A concentric double barrel stainless steel tube was passed via the left carotid artery into the left ventricle under fluoroscopic control and was used to measure left ventricular pressure and dp/dt. Several centimeters proximal to the tip of the inner tube, the outer tube terminated in a second orifice, to which a latex balloon was affixed in such a fashion that on inflation it obstructed the aortic root, thereby imposing a pressure load on the left ventricle.[4,5] Pressures were measured using Sanborn 267BC pressure transducers, and recordings were made on an Electronics for Medicine model DR-8 recorder The animals lay on their right sides, and the zero level for pressure measurements was set at the mid-chest position.

Control pressures and cardiac output were recorded and then steady inflation of the aortic root balloon was carried out over a 30-second interval with continuous recording of left ventricular pressure until aortic pressure distal to the balloon fell to a level of 10 to 20 mm Hg These values are close to the mean circulatory pressure for the entire vascular tree [6] suggesting that obstruction to ventricular outflow was virtually complete. In several instances, absence of ejection of blood was confirmed by injection of indocyanine green dye into the left ventricle and monitoring from the fiberoptic catheter in the aorta. From the left ventricular pressure tracing recorded continuously during the period of occlusion left ventricular peak systolic and end-diastolic pressures were calculated, and plotted against one another to form a pressure-function curve of the left ventricle. [5]

After a 15-minute recovery period pressure and cardiac output measurements were repeated Isoproterenol was infused at the rate of 5 μGm per minute for 3 minutes, then balloon inflation was repeated. Again, a 15-minute recovery period was allowed. Control pressure and cardiac output measurements were made and an infusion of 100 μGm per minute of acetylstrophanthidin was begun Starting at the sixth minute of this infusion balloon inflation was again carried out. For each of these tests, a pressure function curve of the left ventricle was plotted

Following this study the animals were put to death with an overdose of pentobarbital The left ventricle was excised and weighed. The area of infarction was carefully delineated by gross inspection excised and weighed separately Infarct size was then calculated as a percentage of the left ventricle by weight.

Table I Control hemodynamic measurements prior to each occlusion (mean ± SEM)

	Heart rate (beats/min.)	*Cardiac index (L./min./M.²)*	*Aortic mean pressure (mm. Hg)*	*Left ventricular dp/dt (mm. Hg/sec.)*	*Left ventricular end-diastolic pressure (mm. Hg)*
Sham animals					
Initial control	122 ± 8	2 81 ± 0 28	121 ± 8	2 430 ± 240	4 5 ± 1 0
Control following first occlusion	129 ± 9	2 90 ± 0 28	124 ± 8	2 550 ± _50	3 8 ± 1 2
Control following second occlusion	135 ± 9	3 04 ± 0 40	121 ± 8	2 780 ± 330	2 9 ± 0 9
Ligated animals					
Initial control	108 ± 12	2 68 ± 0 31	117 ± 5	2 780 ± 150	11 2 ± 1 7
Control following first occlusion	124 ± 12	2 87 ± 0 35	117 ± 5	2 740 ± 180	9 1 ± 1 3
Control following second occlusion	125 ± 12	2 57 ± 0 29	113 ± 4	2 820 ± 240	7 7 ± 0 9

Results

Under control conditions, prior to any manipulations, there were no significant differences between heart rate, aortic mean pressure, cardiac index, or left ventricular dp/dt between the sham and ligated animals (Table I). However left ventricular end-diastolic pressure was significantly higher in ligated than sham animals ($p < 0.05$). Four of the ligated animals showed a left ventricular end diastolic pressure exceeding 12 mm. Hg with values of 13, 15, 19, and 19 mm. Hg. The repeated control measurements, after the first and second balloon occlusions, showed no significant changes in any of these values (Table I).

A typical left ventricular pressure tracing

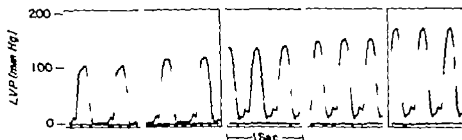


Fig. 1. Sequential one-second strips of left ventricular pressure during inflation of a balloon in the ascending aorta to the point of total obstruction. There is progressive rise in both left ventricular systolic and end-diastolic pressure. During actual measurements, left ventricular end-diastolic pressure was simultaneously recorded on a high gain setting to enhance sensitivity (not shown).

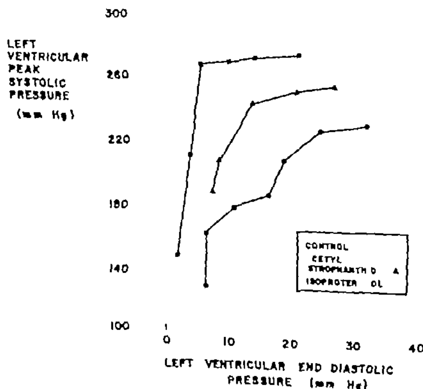


Fig. 2. Pressure function curves in sham animal. Both isoproterenol and acetylstrophanthidin raised the pressure function curve.

during inflation of the balloon in the aortic root is shown in Fig 1 Both systolic and end-diastolic pressures were progressively elevated as obstruction proceeded and form the basis for the pressure function curve. Such a plot of left ventricular peak systolic pressure against left ventricular end-diastolic pressure for 2 individual animals, one a sham and one a ligated animal both during the control state and during isoproterenol and acetylstrophanthidin infusion is shown in Figs. 2 and 3 Each of these curves is characterized by a tendency for left ventricular systolic pressure to rise rapidly at first then as obstruction proceeds to reach a plateau while left ventricular end-diastolic pressure continues to rise to higher levels. In each case, isoproterenol and acetylstrophanthidin shifted the pressure function curve to the left of the control curve indicating the presence of a more forceful contraction at a given left ventricular end-diastolic pressure However in the ligated animal all curves are shifted to the right compared to the sham.

These examples were typical of results obtained in the 2 groups of animals (Figs 4 and 5) The composite curves for sham and ligated animals shown in Figs. 4 and 5 were obtained by combining 2 types of data (1) mean systolic and end-diastolic pressures in the left ventricle prior to obstruction (bottom left point of each curve) and during maximal obstruction (top right point of each curve) and (2) the mean peak systolic pressures at selected diastolic pressures along the rising pressure function curve (mid points along each curve) Considered in this manner both acetylstrophanthidin and isoproterenol raised the pressure function curve in sham animals but the effect of isoproterenol was the more marked (Fig 4) In ligated animals, the control pressure function curve prior to drug administration was shifted to the right compared to the sham animals. Again both isoproterenol and acetylstrophanthidin raised the pressure function curves but in these ligated animals the response to isoproterenol was attenuated and comparable to the re-

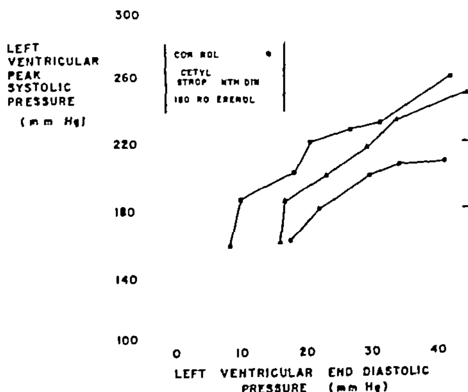


Fig 3 Pressure function curves in a ligated animal. All of the curves are shifted t the right, compared to Fig 2

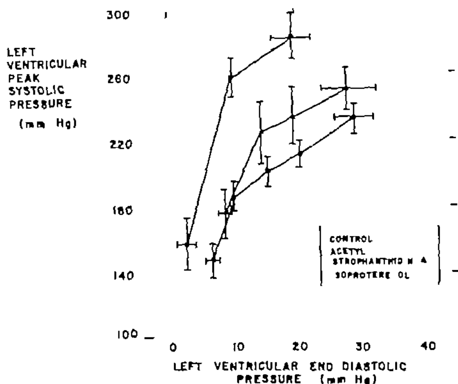


Fig 4 Composite pressure function curves of sham animals.

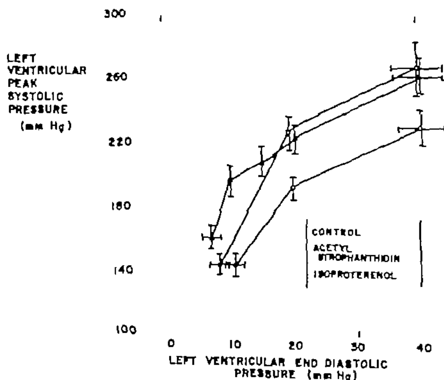


Fig 5 Composite pressure function curves of ligated animals.

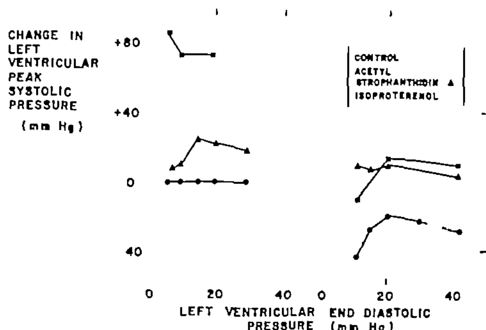


Fig. 6. Composite pressure function curves of sham (left) and ligated (right) animal presented by normalizing the curved control pressure function curve of the sham animals along the zero base line of the graph. All other curves are compared by plotting the pressure differences for each curve in comparison t this normalized base line. The dotted portion of the control line for the ligated animals was obtained by extrapolating the curved ontrol line for the sham animals t comparable left ventricular end diastolic pre-sure

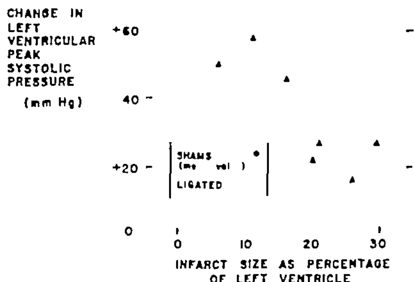


Fig. 7. Comparative incre se in left ventricular peak stolic pressure t a left ventricular end-diastolic pressure of 20 mm. Hg during infusion of isoproterenol, i relation to infarct size. Animal with large infarct showed a reduced pressure response compared to animals with maller infarct and shams.

sponse obtained with acetylstrophanthidin (Fig 5)

In Fig 6, these data are represented in more graphic fashion. In this figure, the curved control line of the sham animals is normalized along the zero base line of the graph. Using this as a reference pressure differences for all other curves are plotted in relation to this line. The striking effect of isoproterenol in sham animals, the depressed base line in ligated animals and the attenuated response to isoproterenol in ligated animals are clearly depicted

It was also noted that the degree of impairment in the pressure function curve in ligated animals with isoproterenol stimulation was related to the relative size of the infarct (Fig 7) Thus with infarcts larger than 20 per cent of the left ventricle the pressure rise induced by isoproterenol at the selected left ventricular end-diastolic pressure of 20 mm. Hg was markedly reduced when compared with that in animals with smaller infarcts.

Discussion

This study was carried out to determine whether defects in left ventricular function can be demonstrated following experimental myocardial infarction. Certain procedures such as close-chested coronary embolization[1] are used to produce acute heart failure in animals, but this technique does not simulate occlusion of a major coronary artery and is not suitable for chronic studies. Chronic congestive failure in animals due to major coronary occlusion is difficult to produce Renais and coworkers[7] observed evidence of congestive failure in dogs following serial ligation of medium-sized coronary vessels, but only a small number of animals survived this procedure.

In the present study ligation of the left anterior descending coronary artery 2 cm. distal to its origin resulted in survival of approximately ⅔ of the animals operated upon. This occurred despite infarction of up to 30 per cent of the left ventricle (Fig 7) Resting hemodynamic measurements in the period 3 to 4 days following infarction were normal except for a modest elevation of left ventricular end-diastolic pressure in several of the animals.[8] However application of a pressure load to the left ventricle and determination of pressure function curves clearly revealed an impairment in the performance of the infarcted ventricle. Under base-line conditions, the pressure function curve for the left ventricle of the animals with infarcts was depressed below that of sham operated animals (Figs. 4 to 6) Furthermore, administration of the inotropic agents acetylstrophanthidin[9] and isoproterenol[10] resulted in further disparity between the pressure function curves of sham and ligated animals (Fig 6) Whereas in sham animals, isoproterenol had a more potent effect in raising the pressure function curve than acetylstrophanthidin in ligated animals the response to these 2 agents was virtually identical (Fig 6) This suggests 2 possibilities (1) that the infarcted ventricle is refractory to exogenously administered catecholamines and (2) that the reserve function of the left ventricle is impaired in animals with infarction, to such an extent that a fixed level of response was obtained with both acetylstrophanthidin and isoproterenol. The data in Fig 7 support the latter possibility for the degree of impairment in response to isoproterenol was more marked in animals with larger infarcts.

The technique of pressure loading the left ventricle to reveal alterations in ventricular function as employed in this study was devised by Goodyer and coworkers.[2] This method possesses the advantages of simplicity and reproducibility and does not result in deterioration of ventricular function provided prolonged obstruction is avoided (Table I) It may be used in the intact close-chested animal. Occasional difficulties were experienced in the form of transient ventricular arrhythmias with the onset of obstruction. These were more common in animals with myocardial infarction but in every instance abated with temporary cessation of balloon inflation so that the curves could be completed. Performance of pressure function curves cannot be considered to be carried out in a constant inotropic milieu, since profound systemic hypotension ensues, and undoubtedly results in activation of baroreceptor reflexes.[11] However hypotension of similar degree was produced in every

instance and evidently the resulting baroreceptor discharge was not intense enough to obscure the inotropic effects of acetyl strophanthidin and isoproterenol (Figs. 4 to 6)

Summary

Pressure function curves of the left ventricle were carried out in dogs with myocardial infarction produced by coronary ligation using the technique of inflating a balloon in the ascending aorta. Under base-line conditions the pressure function curve in animals with infarcts was depressed compared to sham operated animals. Infusion of the inotropic agents acetylstrophanthidin and isoproterenol elevated the pressure function curves in both groups of animals, but the response to isoproterenol was greatly reduced in animals with infarcts. These results show that pressure loading of the left ventricle may be used to reveal defects in ventricular performance in dogs with experimental myocardial infarction in the absence of overt heart failure and that infusion of inotropic agents such as isoproterenol may further accentuate this defect

REFERENCES

1. Agress, C. M Therapy of cardiogenic shock Prog Cardiova Dis 6:236, 1963
2. Harris, A. S. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion Circulation 1:1318, 1950
3. McCarthy B Hood, W B., Jr and Lown, B Fiberoptic monitoring of cardiac output and hepatic dye clearance in dogs, J Appl. Physiol 23:641 1967
4. Goodyer A. V N Goodkind, M J and Landry A. B Ventricular response to a pressure load. Left ventricular function curves in intact animal, Circulation Res. 10:885 1962.
5. Goodyer A. V N Goodkind, M J and Stanley E. J The effects of abnormal concentrations of the serum electrolytes on left ventricular function in the intact animal. Am. Heart J. 67 779 1965.
6. Guyton, A. C Circulatory physiology: cardiac output and its regulation, Philadelphia, 1963, W B Saunders Company p. 197
7. Renais, J Scebat L. and Lenegre J L'ischémie myocardique expérimentale du chien. IV Conséquences hémodynamiques, Arch. mal. Coeur 57:602, 1964
8. Hood W B Jr McCarthy B and Lown, B Myocardial infarction following coronary ligation in dogs. Hemodynamic effects of isoproterenol and acetyl strophanthidin, Circulation Res. 21 191 1967
9. Sarnoff S. J Gilmore J P Wallace A. G., Skinner N S., Mitchell, J H and Daggett W M Effect of acetyl strophanthidin therapy on cardiac dynamics, oxygen consumption and efficiency in the isolated heart with and without hypoxia, Am. J Med. 37:3, 1964
10. Krasnow N Rolett, E. L., Yurchak, P M Hood W B Jr and Gorlin, R Isoproterenol and cardiovascular performance, Am J Med 37:514 1964.
11. Cotton, M DeV and Moran, N C.: Effect of increased reflex sympathetic activity on contractile force of the heart, Am. J Physiol. 191 461 1957

Antiarrhythmic activity of the beta-adrenergic blocking agent 1-isopropylamino-3-(3 tolyloxy)-2 propanol (ICI 45763)

P. Somani, M.B., B.S., Ph.D.
Milwaukee, Wis.

In recent years a new group of drugs classified as beta-adrenergic blocking agents on the basis of their selective inhibition of certain pharmacological effects of catecholamines, has been introduced in experimental medicine. Several specific agents belonging to this category have been synthesized and investigated extensively as pharmacological and physiological tools[1] as well as for possible clinical usefulness. Some of the beta-adrenergic blocking agents, such as pronethalol, propranolol and H56/28[1-(0-allylphenoxy)-3-isopropylamino-2 propanol] have been shown to be effective against both adrenergically and nonadrenergically, especially digitalis-induced cardiac arrhythmias in experimental animals[2-13] as well as in man.[14-15] However, other drugs such as INPEA (n-isopropyl-p-nitrophenylethanolamine) and MJ 1999 {4-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide} are much more specific in suppressing the adrenergically induced arrhythmias.[4,16,17] Theoretically, therefore, it would be useful to employ the latter group of agents in the study of catecholamine-induced arrhythmias in order to avoid the involvement of other mechanisms in the over-all interpretation of their antiarrhythmic activity. In the management of digitalis intoxication, however, a drug with little or no beta-adrenergic blocking activity, and hence a minimal myocardial depression due to inhibition of the sympathetic drive, would be more acceptable than a drug with potent beta-blocking actions.[5,7] Since administration of propranolol in the management of cardiac arrhythmias has been shown to produce a deterioration of cardiac functions and precipitation or aggravation of congestive heart failure with fatal outcome in some cases,[18-22] search for an effective drug with fewer side effects is warranted.

More recently, another potent beta-blocker, 1-isopropylamino-3-(3-tolyloxy)-2-propanol (ICI 45763) (Fig. 1), has been shown to block selectively the positive inotropic, positive chronotropic, and vasodilator response to isoproterenol and was found to be approximately equipotent to propranolol in blocking the beta receptors.[23,24] The same compound was synthesized independently by Engelhardt[25] in Germany and has been designated as Kö 592. The purpose of the present communi-

From the Department of Pharmacology, Marquette School of Medicine, Milwaukee, Wis.
This work was supported by a grant from the Wisconsin Heart Association.
Part of this work was presented at the Fall meeting of the American Society for Pharmacology and Experimental Therapeutics, Washington, D. C., Aug. 27 through 31, 1967.
Received for publication Dec. 29, 1967.

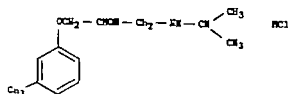


Fig. 1. Structural formula of 1-isopropylamino-3-(3-tolyloxy)-2-propanol (ICI 45763).

cation is to study the spectrum of the antiarrhythmic activity of this agent against a variety of cardiac arrhythmias. Our results show that ICI 45763 is as potent as propranolol in its beta-receptor blocking and antiarrhythmic properties.

Experimental procedures

Experiments were performed in dogs of either sex weighing between 8 and 18 Kg. With the exception of the coronary ligation studies, sodium pentobarbital anesthesia (30 to 35 mg. per kilogram intravenously) supplemented by additional doses as needed was used throughout the experiments. Lead II electrocardiogram (ECG) and carotid artery blood pressure monitored via a Statham P23AC transducer were recorded on a Grass polygraph. The trachea was cannulated and all drugs except methylchloroform were administered into a cannulated femoral vein.

Cardiac arrhythmias were produced by four different methods. (1) Epinephrine-induced ventricular arrhythmias were elicited in a group of five dogs by a rapid intravenous injection of 100 μg per kilogram of the drug. An initial control response to epinephrine was obtained in each animal and the same dose of epinephrine was repeated at 10, 30, 60, and 120 minutes after the administration of ICI 45763. ECG's were analyzed in a manner described previously, in which all beats in each successive 30 second period were counted and classified as sinus or ectopic beats.

The results were graphically represented to show the total number of beats per minute as the sinus and ectopic beats per minute for each successive 30 second period.

(2) Ventricular fibrillation was induced by a combination of methylchloroform and epinephrine. An intratracheal instillation of 0.1 ml. per kilogram of methylchloroform used as a sensitizing agent, was followed 15 to 30 seconds later by a rapid intravenous administration of 10 μg per kilogram of epinephrine. This procedure produced ventricular fibrillation in all of the control animals. In five experiments, the animals were pretreated with ICI 45763 and the initial methylchloroform-epinephrine challenge was given 10 minutes later. Animals which did not develop ventricular fibrillation were rechallenged at 30 minute intervals over a 2 hour period. The incidence of fibrillation observed in the ICI 45763 pretreated group was compared statistically with the incidence of fibrillation observed in the control series by the chi square test with Yate's correction for small numbers.

(3) Ouabain-induced ventricular tachycardia was produced by an initial loading dose of 40 μg per kilogram followed 30 minutes later by 20 μg per kilogram and subsequently 10 μg per kilogram every 15 minutes until a persistent ventricular tachycardia developed. Infusion of ICI 45763 at the rate of 0.5 mg. per kilogram per minute was started 10 minutes after establishment of the arrhythmia and was continued until the arrhythmia was suppressed and a normal sinus rhythm restored.

(4) Ventricular tachycardia was produced by the two stage coronary artery ligation technique of Harris.[17] ICI 45763 (0.5 to 1 mg. per kilogram per minute) was administered to the unanesthetized animals via an indwelling catheter in a femoral vein 18 to 24 hours after coronary ligation and the Lead II ECG's were analyzed for evidence of any changes in the ventricular rhythm.

Results

Epinephrine-induced arrhythmias. The rapid intravenous administration of epinephrine (100 μg per kilogram) produced a run of ventricular arrhythmias which included uni- and multifocal ventricular tachycardia, ectopic premature contractions, and occasional bigeminal rhythm. The arrhythmias usually lasted 3 to 5 minutes following the control injection of epinephrine. Epinephrine-induced cardiac irregularities were diminished or completely

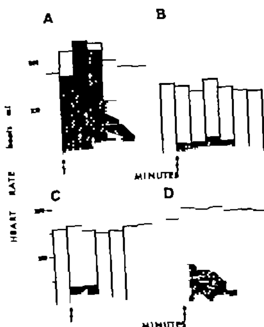


Fig. 2 Antagonism of epinephrine-induced ventricular tachycardia by ICI 45763. Data represent the mean of five experiments. Each bar represents heart rate in beats per minute for each successive 30 second period. The clear portion of each bar represents normal sinus beats; the crosshatched portion represents ectopic beats. Epinephrine (100 μg per kilogram) was administered at 0 time (↑) in each panel. In panel *A* measurements were made prior to the administration of ICI 45763. Panels *B*, *C*, and *D* show the effect of epinephrine at 10, 60, and 120 minutes after 0.5 mg. per kilogram ICI 45763 administration, respectively.

abolished after ICI 45763 (0.5 mg. per kilogram) was given to these animals and the results obtained in a series of five dogs are summarized in Fig. 2. It may be seen that not only the arrhythmogenic but also the positive chronotropic effect of such a large dose of epinephrine was blocked by ICI 45763, thus confirming the beta-adrenergic blocking activity of this agent. The antiarrhythmic effect was maximum 10 minutes after ICI 45763 administration and a gradual increase in the severity of the arrhythmias was observed when subsequent repeated injections of epinephrine were given to these animals. A partial block of the epinephrine induced arrhythmias was still present 2 hours after the administration of ICI 45763.

Ventricular fibrillation induced by methylchloroform and epinephrine. Administration of 10 μg per kilogram of epinephrine 15 to 30 seconds following sensitization of the myocardium by methylchloroform, a halogenated hydrocarbon, resulted in the appearance of ventricular fibrillation in all of the 21 control dogs. The animals in this series include experiments carried out over a period of 4 years. In a second group of five dogs, ICI 45763 (0.5 mg. per kilogram) was infused over a period of 5 minutes prior to the fibrillatory challenge. In the dosage used, ICI 45763 produced a significant reduction ($P < 0.01$) in total heart rate from 139 ± 9 to 115 ± 7 beats per minute with little or no change in the blood pressure. None of the dogs in this series developed ventricular fibrillation when challenged with methylchloroform-epinephrine combination 10 minutes after ICI 45763 administration (Table I), a highly significant difference ($P < 0.001$) as compared by the chi square test. Although the animals pretreated with ICI 45763 did not fibrillate following epinephrine administration, the protection against the methylchloroform-epinephrine combination was not always complete since in many experiments ventricular ectopic beats of different severity and duration were induced by the otherwise fibrillatory challenge. The ventricular arrhythmias increased in severity from few ectopic beats

Table I. Protection against methylchloroform epinephrine ventricular fibrillation by ICI 45763

Drug	No. of total fibrillated/tested*
Control†	21/21
ICI 45763 (0.5 mg./Kg.)	
10 min.‡	0/5
30 min.	2/5
60 min.	2/5
90 min.	3/5
120 min.	3/5
150 min.	5/5

*Animals which did not fibrillate were rechallenged at 30-minute intervals. The data represents cumulative frequency at stated intervals for animals pretreated with ICI 45763.
†Performed over a four year period in conjunction with this [illegible] as well as previous studies.
‡Minutes indicate time after administration of ICI 45763 [illegible].

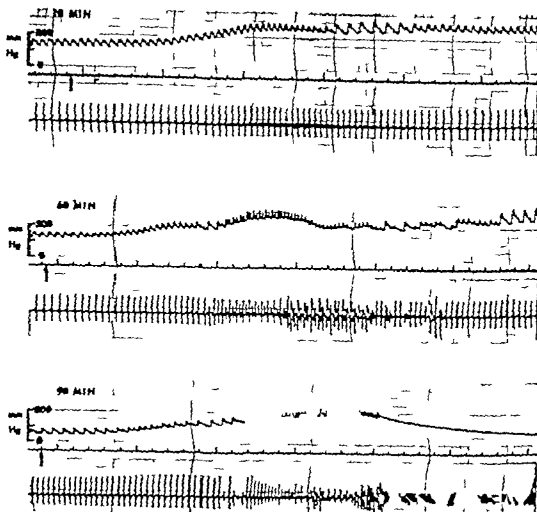


Fig. 1. Protection against methylchloroform-epinephrine fibrillatory challenge by ICI 45763. In each panel, top tracing: arterial pressure; lower tracing: Lead II ECG; time marks: 1 second intervals. Methylchloroform (0.1 ml per kilogram) was administered intratracheally 90 seconds prior to epinephrine (10 μg per kilogram intravenous injection (↑). The methylchloroform-epinephrine challenge produced ventricular fibrillation in each control animal. In this experiment the animal was pretreated with ICI 45763 (0.5 mg per kilogram) 10 minutes prior to the fibrillatory challenge (upper panel). At 60 minutes (middle panel) methylchloroform-epinephrine produced a short run of ectopic ventricular tachycardia but no fibrillation and at 90 minutes (lower panel), the combination produced a brief run of tachycardia followed by fibrillation.

to ventricular tachycardia and ultimately ventricular fibrillation when the animals were rechallenged at different intervals (Fig. 3) although two dogs were still protected against the fibrillatory challenge 120 minutes after ICI 45763 administration (Table I).

Ouabain induced ventricular tachycardia. The ventricular tachycardia produced by toxic amounts of ouabain administered in a graded manner to a group of six dogs was effectively suppressed by an infusion of ICI 45763 (Table II). It may be observed that the mean cumulative dose of ICI 45763 needed to suppress the glycoside induced arrhythmias in these animals was 7.1 ± 0.9 mg per kilogram. The increased heart rate was also reduced significantly by ICI 45763. However, the duration of complete reversion to a normal sinus rhythm by this agent was short and premature ventricular contractions reappeared in five out of the six dogs within 1.5 to 5 minutes (mean = 3.6 ± 0.45 minute). The arrhythmias gradually

Table II Effect of ICI 45763 on ouabain induced ventricular tachycardia

Dog No.	*Control heart rate* (beats/min.)	*Dose ouabain* (µg/Kg)	*Heart rate* *Before* (VT)	*Heart rate* *After ICI 45763* (NSR)	*Dose ICI 45763** (mg/Kg)
1	220	60	188	144	5
2	120	60	192	92	9
3	160	60	204	128	9 5
4	170	60	196	104	9 5
5	124	70	168	124	3
6	168	80	216	132	6
Mean ± S.E.	161 ± 13	65 ± 3	194 ± 7	122 ± 4	7 1 ± 0 9

*Total dose of the drug needed to revert arrhythmia to normal sinus rhythm. VT Ventricular tachycardia and NSR, normal sinus rhythm.

increased in severity in these five dogs and a complete ventricular tachycardia reappeared within 8 to 30 minutes (mean = 23 4 ± minutes) after the end of ICI 45763 infusion (Fig 4) In the remaining experiment, the normal sinus rhythm restored by ICI 45763 persisted for a period of more than 2 hours.

Ventricular tachycardia following two stage coronary artery ligation The effect of ICI 45763 on multifocal ventricular tachycardia resulting from two stage coronary artery ligation was investigated in five dogs. A slow intravenous infusion (0.5 to 1 mg per kilogram per minute) in doses up to 10 mg per kilogram did not suppress the arrhythmia, although a reduction in the total heart rate from 167 ± 7 to 148 ± 5 beats per minute was observed following ICI 45763 administration.

Discussion

Shanks[38] recently reported that ICI 45763 in doses as small as 0.5 mg per kilogram specifically blocked the cardiac stimulant and vasodilator effects of isoproterenol In the present experiments, this new beta adrenergic blocking agent has been found to prevent adrenergically induced multifocal ventricular tachycardia and fibrillation Both the epinephrine and methylchloroform-epinephrine arrhythmias were blocked most effectively at 5 to 10 minutes following ICI 45763 administration and the antiarrhythmic effect gradually decreased over a 2 hour period Like several other beta blockers, such as dichloroisoproterenol (DCI) pronethalol and propranolol [7, 3, 39] ICI 45763 also suppresses cardiac arrhythmias induced by ouabain although the dose necessary to inhibit the latter arrhythmias is much larger than that required to inhibit the other effects mediated through beta receptor stimulation Thus, an average dose of 7 1 mg per kilogram was needed to suppress ouabain-induced as compared to 0.5 mg per kilogram for adrenergically induced arrhythmias. It has been reported previously that the beta-adrenergic blocking agents are ineffective in suppressing the ventricular tachycardia resulting from two stage coronary artery ligation.[8, 9, 39, 40] In the present study ICI 45763 in the dose employed was also found to be ineffective against coronary ligation-induced ventricular arrhythmias. The spectrum of antiarrhythmic activity of ICI 45763 thus appears to be quite similar to that reported for DCI pronethalol and propranolol but differs from that of other specific beta blockers such as INPEA, MJ 1999 and paramethylisoproterenol (PMI) It has been demonstrated previously that INPEA MJ 1999 and PMI which possess specific beta-adrenergic blocking activity suppress only adrenergically induced arrhythmias and are ineffective against other types of arrhythmias.[8, 39, 41]

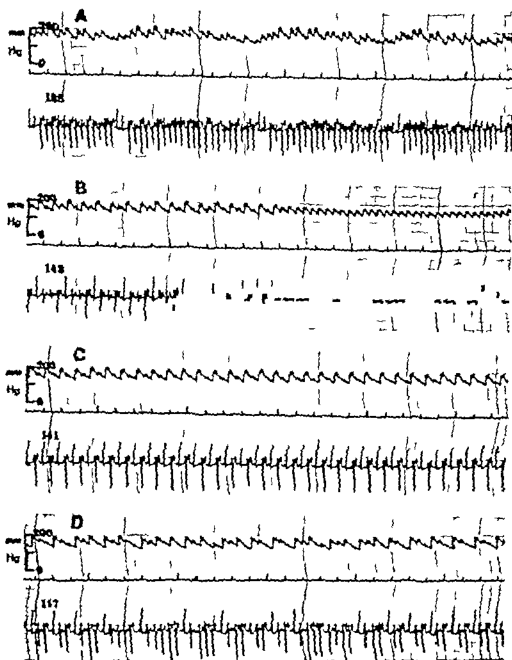


Fig. 4. Effect of ICI 45763 against ventricular tachycardia produced by toxic dose of ouabain. (Tracings from experiment 1.) In each panel, upper tracing: arterial pressure; lower tracing: Lead II ECG; numbers above ECG tracings, heart rate in beats per minute; time marks at 1 second intervals. Panel A: ventricular tachycardia following a cumulative dose of 60 µg per kilogram. Panel B: a gradual reversion of the arrhythmia to a normal sinus rhythm during ICI 45763 infusion. A total dose of 5 mg per kilogram of ICI 45763 was needed to suppress the arrhythmia in this experiment. Panels C and D: the ectopic beats reappeared 5 minutes after the end of ICI 45763 infusion (panel C) and gradually increased to an almost complete ventricular rhythm in 20 minutes (panel D), although the total heart rate is slower than in panel A.

Pronethalol propranolol and ICI 45763 have been found to prolong the refractory period and to reduce the rate of rise and the overshoot of action potential in the guinea pig and rabbit atria.[45-47] These actions, which are classically associated with the effects of the so-called antiarrhythmic drugs[48-49] may account for the suppression of ouabain-induced arrhythmias, although Tuttle and Innes[41] have suggested the possibility of an antidigitalis effect independent of either beta-blocking or quinidine like antiarrhythmic activity

We have previously drawn attention to the fact that all of the known beta blocking agents which suppress arrhythmias produced by digitalis glycosides also possess potent local anesthetic activity whereas the beta-blocking agents which fail to antagonize such arrhythmias also lack the local anesthetic property Although Morales-Aguilerá and Vaughan Williams[44] have shown in the case of both pronethalol and propranolol that no correlation exists between the local anesthetic and antifibrillatory potency such data do not necessarily negate the possibility that there is a close relationship between the two effects. That such a positive correlation may indeed exist is further supported by our results that ICI 45763 suppresses ouabain induced arrhythmias, since it also possesses a local anesthetic activity Likewise, Lucchesi and associates reported that dextro-propranolol which has a very weak beta blocking but potent local anesthetic activity suppressed digitalis-induced arrhythmias. More recently Barrett and colleagues[50] have synthesized another structural analogue of propranolol ICI 50172 and reported that it lacked both antidigitalis and local anesthetic actions but was found to suppress epinephrine-induced arrhythmias.

It is well known that epinephrine alone or in combination with some type of "sensitizing" agent produces cardiac arrhythmias such as ventricular ectopic beats multifocal ventricular tachycardia, or ventricular fibrillation depending upon the dose administered. In recent years, several beta adrenergic blocking drugs such as DCI[51-53] pronethalol,[1 3,54] INPEA MJ 1999[33,34] PMI[4] and propranolol have been reported to suppress cardiac arrhythmias produced by catecholamines. In most of these studies, the dose of the blocking agent necessary to prevent or abolish adrenergically induced arrhythmias was found to be in the same range as that needed to inhibit the positive inotropic and positive chronotropic responses to the catecholamines. The recent experiments by Somani and Lum [32] and Katz and co-workers[5,13] have shown that such an antiarrhythmic action of beta-adrenergic blocking agents is due to a specific blockade at the cardiac beta-receptor sites. In the present experiments, the dose of ICI 45763 necessary to inhibit adrenergically induced arrhythmias was found to be the same as that required to block other beta-receptor responses. These results would seem to indicate that the antiarrhythmic action of this drug in suppressing epinephrine arrhythmias is due to its beta-adrenergic blocking properties However further experiments will be necessary to determine if the antiarrhythmic activity of ICI 45763 is associated with the levo or the dextro rotatory stereoisomer With other beta-adrenergic blocking agents, it has been demonstrated that both the levo and the dextro rotatory isomers suppress ouabain induced arrhythmias, whereas only the levo-isomer antagonizes adrenergically induced arrhythmias in the dose that inhibits the beta receptors.[7 13]

Propranolol has been used successfully in the clinical management of cardiac arrhythmias due to catecholamines and digitalis glycosides. [54] Administration of propranolol however may cause a deterioration of cardiac function due to both a direct depressant action and due to blockade of sympathetic stimulant effects on the myocardium [7-50,57-4] ICI 45763 on the contrary produced little direct myocardial depression since its negative inotropic effect was almost completely abolished by reserpine pretreatment.[42] It will be interesting to see if this agent will differ significantly from propranolol in its myocardial depressant effects in the clinical practice.

Summary

The antiarrhythmic activity of 1-isopropylamino 3-(3 tolyloxy) 2 propanol (ICI 45763) a new beta-adrenergic blocking agent was investigated against different types of cardiac arrhythmias in the dog ICI 45763 in a 0.5 mg per kilogram dose

effectively blocked the positive chronotropic action of epinephrine and protected the animals against the ventricular tachycardia and ventricular fibrillation produced by epinephrine. An average dose of 7.1 mg. per kilogram of ICI 45763 was needed to suppress ventricular tachycardia by toxic doses of ouabain and this agent was ineffective against the ventricular arrhythmias resulting from two stage coronary artery ligation in doses up to 10 mg. per kilogram. ICI 45763 resembles other beta adrenergic blocking agents which suppress both adrenergically induced and ouabain induced arrhythmias and the mechanism of suppression of the two types of arrhythmias appears to be different.

The author wishes to acknowledge the excellent technical help of M. Wyne Herrick. A generous supply of ICI 45763 was provided through the courtesy of Imperial Chemical Industries Ltd., England.

REFERENCES

1. Moran, N. C., editor: New adrenergic blocking drugs, Ann. New York Acad. Sc. 139:545, 1967.
2. Braunwald, E., editor: Symposium on beta adrenergic receptor blockade, Am. J. Cardiol. 18:303, 1966.
3. Sekiya, A., and Vaughan Williams, E. M.: The effects of pronethalol, dichloroisoproterenol and disopyramide on the toxicity to the heart of ouabain and anesthetics, Brit. J. Pharmacol. 21:462, 1963.
4. Erlij, D., and Mendez, R.: The modification of digitalis intoxication by excluding adrenergic influences on the heart, J. Pharmacol. & Exper. Therap. 144:97, 1964.
5. Lucchesi, B. R.: The action of Nethalide upon experimentally induced cardiac arrhythmias, J. Pharmacol. & Exper. Therap. 145:286, 1964.
6. Somani, P., and Lum, B. K. B.: The antiarrhythmic actions of beta adrenergic blocking agents, J. Pharmacol. & Exper. Therap. 147:194, 1965.
7. Lucchesi, B. R.: The effects of pronethalol and its dextro isomer upon experimental cardiac arrhythmias, J. Pharmacol. & Exper. Therap. 148:94, 1965.
8. Katz, R. L.: Effects of alpha and beta adrenergic blocking agents on cyclopropane-catecholamine cardiac arrhythmias, Anesthesiology 26:289, 1965.
9. Lucchesi, B. R., Whitsitt, L. S., and Brown, N. L.: Propranolol (Inderal) in experimentally induced cardiac arrhythmias, Canad. J. Physiol. Pharmacol. 44:543, 1966.
10. Sharma, P. L.: Effect of propranolol on catecholamine induced arrhythmias during nitrous oxide-halothane anesthesia in the dog, Brit. J. Anaesth. 38:871, 1966.
11. Somani, P., and Bachand, R. T., Jr.: Antiarrhythmic actions of propranolol in the ... heart-lung preparation, Am. Heart J. ..., 1967.
12. Dunér, B. R., Garberg, L., and Johansson, B.: The effect of propranolol and the dextro and levo isomers of H 56/28 on ouabain induced ventricular tachycardia in unanesthetized ... Acta pharmacol. toxicol. (Suppl. 2) 25:41, 19...
13. Katz, R. L., Lord, C. O., and Eakins, K. E.: Anesthetic-dopamine cardiac arrhythmias and their prevention by beta adrenergic blockade, J. Pharmacol. & Exper. Therap. 158:40, 19...
14. Stock, J. P. P., and Dale, N.: Beta adrenergic receptor blockade in cardiac arrhythmias, Brit. M. J. 2:1230, 1963.
15. Johnstone, M.: Beta-adrenergic blockade with pronethalol during anesthesia, Brit. J. Anaesth. 36:224, 1964.
16. Payne, J. P., and Senfield, R. M.: Pronethalol in treatment of ventricular arrhythmias during anaesthesia, Brit. M. J. 1:603, 1964.
17. Hellewell, J., and Potts, M. W.: Propranolol and ventricular arrhythmias with halothane, Anaesthesia 20:269, 1965.
18. Besterman, E. M. M., and Friedlander, D. H.: Clinical experiences with propranolol, Postgrad. M. J. 41:526, 1965.
19. Rowlands, D. J., Howitt, G., and Markman, P.: Propranolol (Inderal) in disturbances of cardiac rhythm, Brit. M. J. 1:891, 1965.
20. Sloman, G., Robinson, J. S., and McLean, K.: Propranolol (Inderal) in persistent ventricular fibrillation, Brit. M. J. 1:895, 1965.
21. Harrison, D. C., Griffin, J. R., and Fiene, T. J.: Effects of beta adrenergic blockade with propranolol in patients with atrial arrhythmias, New England J. Med. 273:410, 1965.
22. Luria, M. H., Adelson, E. I., and Miller, A. J.: Acute and chronic effects of an adrenergic beta receptor blocking agent (propranolol) in treatment of cardiac arrhythmias, Circulation 34:767, 1966.
23. Turner, J. R. B.: Propranolol in the treatment of digitalis-induced and digitalis resistant tachycardias, Am. J. Cardiol. 18:450, 1966.
24. Harrison, D. C., and Griffin, J. R.: The antiarrhythmic effects of propranolol, Ann. New York Acad. Sc. 139:997, 1967.
25. Somani, P., and Lum, B. K. B.: Blockade of epinephrine and ouabain induced cardiac arrhythmias in the dog heart lung preparation, J. Pharmacol. & Exper. Therap. 152:235, 1966.
26. Somani, P., Fleming, J. G., Chan, G. K., and Lum, B. K. B.: Antagonism of epinephrine induced cardiac arrhythmias by 4-(2-isopropylamino-1-hydroxyethyl) methanesulfonanilide (MJ 1999), J. Pharmacol. & Exper. Therap. 151:32, 1966.
27. Parmley, W. M., and Braunwald, E.: Comparative myocardial depressant and antiarrhythmic properties of d-propranolol, dl-propranolol and quinidine, J. Pharmacol. & Exper. Therap. 158:11, 1967.
28. Sowton, E., and Hamer, J.: Hemodynamic changes after beta adrenergic blockade, Am. J. Cardiol. 18:317, 1966.
29. Bath, J. C. J. L.: Treatment of cardiac arrhyth...

mias in unanesthetized patients. Role of adrenergic beta receptor blockade, Am. J Cardiol. 18:415 1966.
30. Sarkar, P Jackson, F Wynne, N. A., Vohra, J K., Batson, G A., and Dow W I M Clinical observations on the use of propranolol in disorders of cardiac rhythm, Am. J Cardiol. 18:426 1966
31 Schamroth L Immediate effects of intravenous propranolol on various cardiac arrhythmias, Am. J Cardiol. 18:438, 1966.
32. Stephen, S. A U wanted effects of propranolol, Am. J Cardiol. 18:463 1966
33. Wolfson S Robbins, S. I and Krasnow N Treatment of cardiac arrhythmias with beta adrenergic blocking agents, clinical and experimental studies, Am. Heart J 72 177 1966.
34 Shanks, R. G. The peripheral vascular effects of propranolol and related compounds, Brit. J Pharmacol. 29:204 1967
35 Kanmann, A. J and Blinks, J R Sympathomimetic and non-sympathomimetic stimulant effects of β-adrenergic blocking agents on isolated heart muscle Pharmacologist 9:248, 1967
36. Engelhardt, A Methode zur Auswert ng von β-Adrenolytica am isolierten Herzvorhof Arch exper P th. Pharmakol 249:237 1965
37 Harris, A. S Delayed development of ventricular ectopic rhythms following experimental coronary occlusion Circulation 1 1318, 1950
38. Aronsty J J and Cohen, J The effect of a β-adrenergic blocking agent, pronethalol, on digitalis-induced entricular arrhythmias, Am Heart J 71:503, 1966.
39 Moran, N C Moore, J L, Holcomb, A K and Mushet, G. A tagonism of adrenergically induced cardiac arrhythmias by dichloroisoproterenol, J Pharmacol & Exper Therap. 136:327 1962.
40. Shanks, R G and Dunlop, D Effect of propranolol on arrhythmias following coronary artery occlusion in dogs Cardiovasc Res 1:34 1967
41 Corrodi, H., Persson, H Carlsson, A and Roberts, J A new series of substances hich block the adrenergic β-receptors, J Med. Pharm. Chem. 6 751 1963
42. Kurchlinsky G and Rahn, K H U ter suchungen über die Beziehungen zwischen chinidinartigen und β-adrenolytischen Wirkungen von 1-(3-Methylphenoxy)-2-hydroxy 3-isopropylaminopropan (KÖ 592) Arch exper Path Pharmakol 252:50, 1965
43. Sekiya, A and Vaughan Williams, E. M A comparison of the antifibrillatory actions and effects on intracellular cardiac potentials of pronethalol, disopyramide nd quinidine, Brit J Pharmacol. 21:473, 1963
44 Morales-Aguilerá, A., and V ughan Williams, E. M The effect on cardiac muscle of beta-receptor antagonists in relation to their activity as local anesthetics, Brit. J Pharmacol. 24:332, 1965.
45 Benfey B G and Varma, D R. Antisympathomimetic and antifibrillatory effects of pronethalol and propranolol, Brit. J Pharmacol 26:3 1966.
46. Hoffman, B F and Singer D H. Appraisal of the effects of catecholamines on cardiac electrical activity Ann. New York Acad Sc. 139:914, 1967
47 Engstfeld, G. Der einfluss des Beta-Receptor blockers Propranolol auf die experimentell induzierte Schrittmacher Aktivität isolierten Myokard Präparate Arch. exper P th. Pharmakol. 258:266, 1967
48. Dawes, G. S. Experimental cardiac arrhythmias and quinidine-like drugs, Pharmacol. Rev 4:43 1952
49 Hoffman, B F and Cranefield, P F Electrophysiology of the heart, New York, 1960, McGraw Hill Book Co Inc.
50. Vaughan Williams, E. M Mode of action of beta receptor antagonists on cardiac muscle Am. J Cardiol. 18:399 1966
51 Tuttle, R. R and Innes, I R I teraction of pronethalol and ouabain on cardiac rhythm and automaticity J Pharmacol. & Exper Therap. 153:211 1966.
52. Barrett, A. M Crowther A. W D nlop, D Shanks, R. G., and Smith L. M Cardioselective β-blockade paper presented t the Summer Meeting of British and German Pharmacological Societies, Cambridge September 1967
53 Gilbert, J L Lange G and Brooks, C. McC. Influence of sympathomimetic drugs on ar rhythmias caused by m ltiple stimuli, Circulation Res. 7:417 1959
54 Moore, J I and Swain, H H Sensitization t ventricular fibrillation. I Sensitization with substituted propiophenone, U-0882, J Pharmacol. & Exper Therap 128:243 1960.
55 Sutter M C and Dresel, P E Mechanism of selective blockade of cyclopropane-adrenaline cardiac arrhythmias by dichloroisoproterenol, Canad. J Biochem. 39 1783 1961
56 Murray J W Mcknight, R. L. and Davis, D Antagonism of hydrocarbon anesthetic-epinephrine arrhythmias in dogs by Nethalide, a dichloroisoproterenol analog, Proc Soc. Exper Biol. & Med 113:439 1963
57 Levy J V and Richards, V Inotropic and chronotropic effects of a series of β-adrenergic blocking drugs some structure-activity relationships, Proc. Soc. Exper Biol. & Med 122:373, 1966.
58 Blinks, J R Evaluation of the cardiac effects of several beta adrenergic blocking agents, Ann New York Acad. Sc. 139:673, 1967
59 Levy J V Catecholamine stores and the negative inotropic effect of beta adrenergic blocking drug on the isolated abbit heart, Arch. I t Physiol 75:381 1967

Studies on isoproterenol induced cardiomegaly in rats

Hubert C Stanton Ph.D
*George Brenner B S***
Ernest D Mayfield Jr Ph.D
Houston Texas

Cardiomegaly in rats resulting from massive doses of isoproterenol (ISO) (80 mg per kilogram subcutaneously administered twice daily for 2 days) involves cardiac edema followed by increases in cardiac protein and nucleic acids. Severe, grossly detectable myocardial lesions were also noted with this ISO dose. Since maximal cardiac enlargement was elicited by ISO (5 mg per kilogram) a dose which induced minimal grossly detectable myocardiopathies, we postulated that this might serve as a model for conveniently studying the development of cardiac hypertrophy under a variety of conditions. The following experiments were therefore undertaken to compare ISO dosage and treatments on the development of cardiac lesions and cardiomegaly Biochemical alterations related to cardiomegaly were also evaluated during the treatment in order to compare the results of this study with those obtained with other cardiac hypertrophy models.

Methods

Female Wistar rats weighing 190 to 250 Gm were used in these studies. Three animals were housed in each cage and received a standard laboratory diet and tap water ad libitum

Tissue weight. Hearts were removed from rats anesthetized with pentobarbital sodium (50 mg per kilogram intraperitoneally) The atria were removed and the ventricles rinsed with either 0.25 molar sucrose or 0 9 per cent sodium chloride solution (depending upon whether electrolytes were to be assayed) Dry weights were determined in tissues dried at 115° C. in a forced draft oven and stored in a desiccator Lipids were extracted with chloroform methanol (3 1) Heart weights were adjusted to a common body weight by analysis of covariance.

Blood pressure determinations Blood pressure was determined in unanesthetized rats from chronically indwelling aortic catheters[1] The animals were lightly restrained in a towel during the recording but were free at other times. Heart rates were taken from the blood pressure records.

Electrolytes Dried fat free ventricles were extracted at least 96 hours in 10 ml. of 1 N nitric acid at 4 C. Na^+ and K^+ were determined by emission flame photometry

With the technical assistance of C. M. Cooper E. Bowman, and J Frega.
From the Departments of Pharmacology and Pathology Baylor University College of Medicine, Houston, Texas.
Supported by the United States Public Health Service Grants HE 10531 and HE 05435-07 projects 6 and 8 and grant from the Texas Heart Association. Computer services were supported by United States Public Health Service Grant FR 00254.
Received for publication Jan. 12, 1968.
Address: Department of Pharmacology Baylor University College of Medicine, 1200 Moursund Avenue, Houston, Texas 77025.
**Predoctoral trainee in Pharmacology GM/670 from the National Institute of General Medical Sciences.

(Baird Atomic Model KY3) Mg^{++} and Ca^{++} were estimated by atomic absorption flame photometry (Perkin Elmer Model 303) using a lanthanum carrier Cl was determined with a chloridometer (Buchler Cotlove) Extracellular space was estimated from tissue and plasma Cl values by standard methods.[3]

Nucleic acid determination Total ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) were determined in hearts taken from rats anesthetized with sodium pentobarbital (50 mg per kilogram intraperitoneally) The ventricles were homogenized in cold 0 25 molar sucrose and the nucleic acids extracted by a modification of the Schmidt and Thannhauser procedure. The concentration of RNA was determined spectrophotometrically (260 mμ) by comparing the absorption of the extract with appropriate standard solutions of purified yeast RNA.* DNA was determined by the diphenylamine reaction using calf thymus DNA as a standard. Protein was determined by the method of Lowry and associates.[4]

Incorporation of C^{14}-labelled amino acids Reconstituted C^{14} protein hydrolysate† (5μc/100 grams of body weight) was injected into the exposed jugular vein of rats lightly anesthetized with ether Three hours later the animals were anesthetized with sodium pentobarbital (50 mg per kilogram intraperitoneally) and the ventricles were rapidly removed, rinsed and homogenized (5 per cent) in distilled water Protein was precipitated from 2 ml. of the homogenate with 10 per cent trichloroacetic acid Lipids were removed with 95 per cent ethanol containing 10 per cent potassium acetate, absolute ethanol-diethyl ether (3 1) and diethyl ether Nucleic acids were removed by heating the precipitate at 90° C for 45 minutes in 0.5 N perchloric acid (PCA)[4] The remaining protein was dissolved in 1 ml. of Nuclear Chicago solubilizing agent (NCS) The sample was added to 10 ml. of scintillation media (0.5 per cent 2,5-diphenyloxazole in toluene) and the radioactivity determined and corrected for quenching using a Beckman scintillation spectrometer A sample of skeletal muscle (gastrocnemius) was treated in the same manner as a reference tissue.

Catecholamines Hearts removed from rats anesthetized with sodium pentobarbital (50 mg per kilogram intraperitoneally) were homogenized in 0 4 N PCA. Catecholamines were determined as described by Anton and Sayre[7] using an Aminco-Bowman spectrophotofluorometer

Statistical analyses were performed by standard methods using an IBM digital computer

Results

Cardiac enlargement ISO (5 mg per kilogram subcutaneously) elicited maximal cardiac enlargement when administered twice daily for 10 days (Fig 1,*A*) The final body weights of all animals were similar (252 to 268 grams) and all rats including controls exhibited weight gains of 16 to 25 grams The mortality rate during the 10 day treatment was low and not related to ISO dosage (control = 0/10 ISO 0 1 mg per kilogram = 1/10 ISO 1 0 mg per kilogram = 3/10 ISO 5 0 mg per kilogram = 2/10 ISO 20 mg per kilogram = 1/10 and ISO 80 mg per kilogram = 1/10.

Fig 1,*B* illustrates the effect of increasing the duration of ISO (5 mg per kilogram subcutaneously) treatment on per cent change in cardiac wet and dry weight. Two doses were injected daily and the animals were put to death 17 hours after the last dose. Rats treated with 1 dose of ISO were put to death after 24 hours. Significant cardiomegaly did not occur in rats receiving less than 4 doses of ISO (5 mg per kilogram subcutaneously) within 2 days. Both wet and dry cardiac weights increased indicating new protein deposition although wet weight increased more on a percentage basis, suggesting edema. These differences were more apparent during the earlier stages of treatment.

Ventricles, obtained from rats which had been treated with multiple doses of ISO (5 mg per kilogram subcutaneously) exhibited pale apical regions but not

*Sigma Chemical Co.
†Schwarz Bioresearch Labs, Inc., Orangeburg, N. Y

*Polytron, Brinkmann, Instruments, Westbury N. Y.

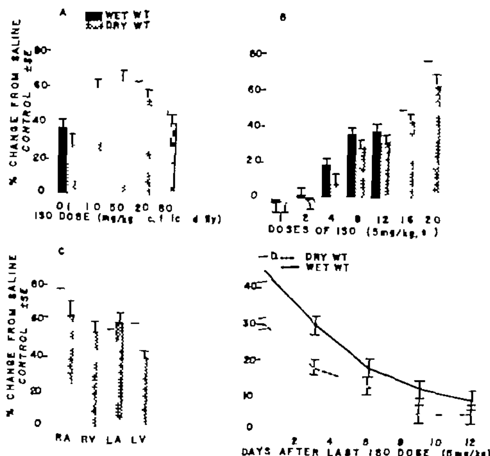


Fig. 1. *A*. Per cent increases in cardiac wet and dry weights following varying doses of ISO administered twice daily for 10 days. Seven to 10 rats per dose. S.E. refers to standard error. *B*. Per cent increases in cardiac wet and dry weights following variable number of doses of ISO 5 mg. per kilogram administered twice daily. Eight to 10 rats per group. *C*. Per cent increases in wet and dry weights of right (*R*) and left (*L*) atria (*A*) and ventricles (*V*) induced by ISO 5 mg. per kilogram, subcutaneously administered twice daily for 4 days. The ordinate represents per cent increase from control. Six to 8 rats per group. *D*. The effect of discontinuing ISO administration upon cardiac wet and dry weights. The per cent increases from control 17 hours after ISO 5 mg. per kilogram subcutaneously administered twice daily for 4 days, are represented by 0 days. Six to 8 rats per group.

severe gross, necrotic lesions observed with larger doses (80 mg. per kilogram subcutaneously). Microscopic lesions (hematoxylin and eosin) were apparent in all hearts taken from ISO (5 mg. per kilogram) treated rats. After 1 dose the lesions consisted of histiocytes with a few fibroblasts localized in the subendocardial portions of the apex and papillary muscles. Apical lesions became more confluent and focal lesions appeared in other areas such as the right ventricle with prolonged ISO treatment. Since these effects of ISO have been well documented by others photomicrographs of the tissues were not included.

Atria and ventricles were both enlarged after ISO (5 mg. per kilogram subcutaneously) administered twice daily for 4 days (Fig. 1,*C*). The per cent increases in wet or dry weights of the right or left atria and right ventricle were not significantly different although the left ventricular wet weight (including septum) was increased more on a per cent basis ($P < 0.05$) than dry weight.

The size of the heart decreased after cessation of ISO (5 mg. per kilogram, subcutaneously administered twice daily for 4 days) treatment (Fig. 1,*D*).

Propranolol administered 30 minutes before each ISO injection partially pre-

Ayerst Laboratories, New York, N. Y.

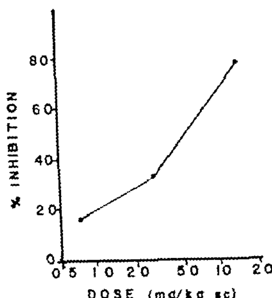


Fig. 2. The ordinate represents propranolol antagonism (per cent inhibition) of the cardiomegaly induced by ISO 5 mg. per kilogram subcutaneously administered twice daily for 4 days. The abscissa represents log doses of propranolol administered 30 minutes before each ISO injection. Six to 8 rats per point.

vented cardiomegaly. Fig. 2 illustrates the relationship between the log dose of propranolol and the per cent inhibition of ISO-induced increases in wet heart weight. The propranolol doses represent, respectively, propranolol: dl-ISO molar ratios of 1.8, 1.2, and 2.1. The per cent inhibition of ISO-induced cardiomegaly by propranolol was calculated as follows: 1.00 − [wet heart weight (ISO control) − wet heart weight (ISO and propranolol)/wet heart weight (ISO control) − wet heart weight (saline control)] × 100 = per cent inhibition.

Blood pressure and heart rate. The administration of ISO (5 mg. per kilogram subcutaneously) to unanesthetized rats with chronically indwelling aortic catheters resulted in hypotension and persistent tachycardia (Fig. 3). These responses were quantitatively similar with ISO doses ranging from 1 to 80 mg. per kilogram subcutaneously and there was no apparent dose-dependent relationship within this dose range. The duration of maximal tachycardia may have been longer with the 80 mg. per kilogram than with the 5 mg. per kilogram dose. However, the variability of this parameter in unanesthetized rats was extensive and reliable comparisons of duration were not possible.

Electrolytes. Adjusted wet heart weight, total and extracellular water, Na^+, Ca^{++}, and Cl^- increased with increasing ISO dosage (1, 5, and 80 mg. per kilogram administered twice daily for 2 days). K^+ contents were greater than control after 1 and 5 mg. per kilogram but less than control after 80 mg. per kilogram. Mg^{++} contents were reduced to the same extent by all ISO doses. These results are summarized in Table I with the statistical significance of each measurement. The cardiac water or electrolyte contents were not further altered by ISO 5 mg. per kilogram administered twice daily for 4 days instead of 2 days. However, the hearts were significantly larger after the more prolonged treatment.

Nucleic acids. The effects of multiple doses of ISO (5 mg. per kilogram subcutaneously) upon the concentrations (milligram per gram) and levels (milligram per heart) of cardiac nucleic acids and proteins are shown in Tables II and III. Heart wet weight increased progressively with the number of ISO treatments but the slightly elevated protein concentrations were not statistically significant. The levels of protein in each heart increased ($P < 0.05$) after 4 or more doses of ISO. DNA concentrations (milligram per gram) remained constant although the levels in each heart increased significantly after 8 or more ISO injections. The contents of RNA in terms of either milligram per gram or milligram per heart were significantly elevated by ISO treatment. The maximal increases in RNA content and RNA/DNA ratios occurred after 8 doses. RNA and DNA levels per heart were greater after 4 doses of 80 mg. per kilogram of ISO than after 5 mg. per kilogram (RNA = 3.42 vs. 2.77 mg. per heart; DNA = 1.31 vs. 1.14 mg. per heart).

Incorporation of C^{14} amino acids into protein. ISO 1, 5, and 80 mg. per kilogram administered twice daily for 2 days significantly enhanced the incorporation of C^{14} labelled amino acids (as protein hydrolysate) into cardiac protein (Fig. 4,A)

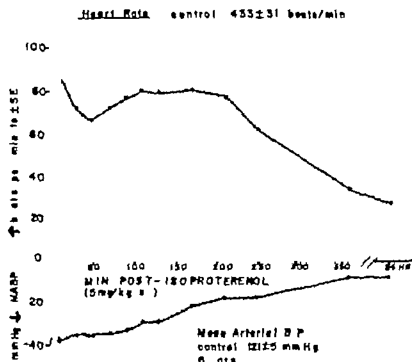


Fig. 3 Increases in heart rate per minute and decreases in mean arterial blood pressure (millimeters of mercury) induced by ISO 5 mg per kilogram subcutaneously in unanesthetized rats with indwelling aortic catheters. The stippled areas represent the boundaries of standard error

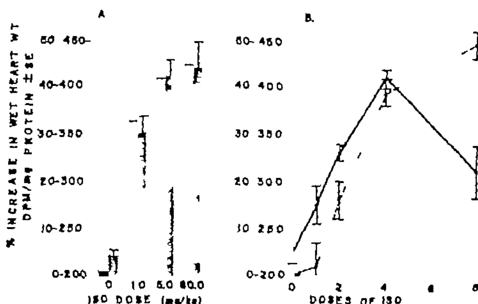


Fig 4 A Relationships between per cent increases in cardiac wet weight (solid bars) and incorporation (d.p.m. per milligram protein) of C^{14}-labelled amino acids into cardiac protein (stippled bars), induced by increasing doses of ISO administered twice daily for 2 days. Six to 8 rats per group. B Relationship between per cent increases in cardiac wet weight (broken line) and the incorporation of C^{14} labelled amino acid (solid line) into cardiac protein following increasing numbers of doses of ISO 5 mg per kilogram. Five to 8 rats per point.

Table I. Cardiac electrolyte and water content after ISO treatment

Parameter measured	ISO dose (mg./Kg. subcutaneously)			
	Control	1	5	10
No. of rats	5	9	5	8
Wet weight (mg.)	753 ± 35	814 ± 22†	840 ± 34†	940 ± 30†
Total H_2O (Gm./Kg.)	775 ± 1	790 ± 3†	798 ± 1†	811 ± 2†
Extracellular H_2O (Gm./Kg.)	207 ± 13	258 ± 16†	276 ± 9†	348 ± 16†
Na (mEq./Kg. FFDS)	221 ± 17	232 ± 7	263 ± 7†	266 ± 13†
K (mEq./Kg. FFDS)	405 ± 3	459 ± 6†	445 ± 6†	373 ± 5†
Ca^{++} (mEq./Kg. FFDS)	9.8 ± 0.4	10.5 ± 0.5	12.3 ± 0.5	15.0 ± 1.8†
Mg^{++} (mEq./Kg. FFDS)	85 ± 2	73 ± 1†	74 ± 1†	74 ± 1†
Cl^- (mEq./Kg. FFDS)	115 ± 5	125 ± 5	147 ± 6†	203 ± 8†

FFDS, fat free dry solids.
*Administered twice daily for 2 days.
†Significantly different than control (P < 0.05).

Table II. Nucleic acid and protein concentrations in the heart muscle after ISO treatment

No. of ISO 5 mg./Kg. doses	No. of rats	Wet heart wt. (mg. ± S.E.)	Protein mg./Gm. ± S.E.	DNA mg./Gm. ± S.E.	RNA mg./Gm. ± S.E.
0 (control)	13	677 ± 25	139 ± 4	1.39 ± 0.04	2.19 ± 0.08
2 (1 day)	8	808 ± 33	131 ± 5	1.36 ± 0.07	2.51 ± 0.10
4 (2 days)	8	870 ± 36	138 ± 3	1.22 ± 0.04	3.00 ± 0.09*
8 (4 days)	6	918 ± 40*	156 ± 3	1.29 ± 0.02	3.44 ± 0.06
12 (6 days)	8	981 ± 35	135 ± 7	1.36 ± 0.06	2.94 ± 0.17
16 (8 days)	8	1,073 ± 23	151 ± 5	1.17 ± 0.02	2.91 ± 0.04

*Significantly different (P < 0.05) from 0.9 per cent NaCl control.

The extent of incorporation increased as the wet weight of the heart increased. The degree of C^{14} amino acid incorporation into cardiac protein also increased with the number of doses of ISO (5 mg. per kilogram subcutaneously) administered (Fig. 4,B). However, the incorporation was not as great after 8 doses of ISO (4 days) as after 4 doses (2 days) even though wet weight and total protein continued to increase. These incorporation experiments were started 24 hours after a single ISO injection or 17 hours after the last multiple dose of the drug. The total amount of protein (milligram per heart) increased with the number of ISO treatments or doses. Incorporation of C^{14} amino acids into skeletal muscle proteins (gastrocnemius) was not altered by ISO treatment in these rats.

Five animals were treated with cyclohexamide (0.2 mg. per kilogram, subcutaneously) and ISO (5 mg. per kilogram subcutaneously) administered twice daily for 2 days. The cyclohexamide was administered 1.5 hours after the first and 1.5 hours before the second daily dose of ISO. The incorporation of C^{14} labelled amino acids into cardiac protein (control ISO = 412 vs. cyclohexamide + ISO = 327 d.p.m. per milligram of protein) was partially inhibited ($P < 0.05$).

Cardiac catecholamines. Total cardiac catecholamine concentration (microgram per gram) decreased proportionately ($P < 0.05$) as the size of the heart increased

Table III Total protein and nucleic acid levels in each heart after ISO treatment

N of ISO 5 mg./Kg. doses	Protein mg./heart ± S.E.	DNA mg./heart ± S.E.	RNA mg./heart ± S.E.
0 (control)	94 ± 6	0 98 ± 0 09	1 57 ± 0 08
2 (1 day)	103 ± 6	1 05 ± 0 05	1 97 ± 0 11
4 (2 days)	127 ± 5	1 14 ± 0 05	2 77 ± 0 1**
8 (4 days)	151 ± 8	1 24 ± 0 04	3 33 ± 0 15
12 (6 days)	145 ± 10*	1 28 ± 0 07*	2 79 ± 0 25*
16 (8 days)	159 ± 4	1 18 ± 0 02	3 07 ± 0 08*

*Significantly different (P 0 05) from 0 9 per cent NaCl treated control.

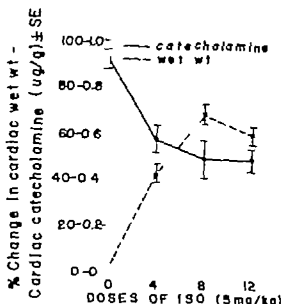


Fig 5 Relationships between cardiac wet weight (per cent increase) and heart catecholamine content (microgram per gram) following increasing numbers of doses of ISO 5 mg per kilogram, administered twice daily Five to 8 rats per point

following multiple doses of ISO (Fig 5) The levels (microgram per heart) of catecholamine did not change (control = 0 56 ± 0 02 μg ISO 4 doses = 0 50 ± 0 04 μg ISO 8 doses = 0 50 ± 0 06 μg and ISO 12 doses = 0 48 ± 0 06 μg)

Discussion

ISO in doses which elicited cardiomegaly also induced microscopically and in some instances grossly detectable, infarctlike lesions. Although we did not quantitate the magnitude of these lesions, other studies conducted in this laboratory[4] as well as in others,[4] have demonstrated the severity of damage increased with ISO dosage. Biochemical changes measured in the heart after various ISO doses and treatments may reflect a balance between inflammation on one hand and tissue repair or viable tissue compensation on the other Since the entire ventricles were studied dilution of viable with injured myocardium may have also influenced the chemical measurements. In spite of these complexities, certain generalities concerning the development of ISO induced cardiomegaly emerge from these studies. (1) Cardiac edema and protein deposition are both involved. Manifestations of edema (increased total and extracellular water) which occurred early in the development of the cardiomegaly agree with histological findings. (2) The electrolyte changes encountered with ISO 80 mg per kilogram agree with those reported by Lehr and associates[1] who also noted increases in cardiac water Na^+ and Ca^{++} but decreases in K^+ and Mg^{++} after massive doses of the drug An explanation for the increase in cardiac K^+ after ISO 1 or 5 mg per kilogram and the decrease after ISO 80 mg per kilogram is not apparent However this increase persisted even though ISO (5 mg per kilogram) treatments were extended to 4 days. (3) The increased cardiac protein deposition and synthesis, as well as augmented nucleic acid contents, resemble qualitatively the observations of other investigators who have studied cardiomegaly of other origins. [18] In the rat salivary gland hyper

rophy may be induced by ISO administration frequent amputation of incisor teeth or intrabuccal administration of papain. In each of these instances the nucleic acid and protein changes resemble those seen in the heart following ISO treatment lesions do not accompany the hypertrophy of the glands.[illegible] (4) Both RNA and DNA levels increased with the development of ISO-induced cardiomegaly although RNA was elevated more than DNA (RNA/DNA ratios were increased. This may suggest that myocardial fiber growth (hypertrophy) contributes more to the cardiomegaly than hyperplasia. Korecky and French[9] reported that in cardiomegaly (approximately 100 per cent larger than control) induced in rats with iron deficiency RNA/DNA ratios did not change but RNA and DNA levels in each heart increased. This enlargement was therefore attributed to hyperplasia. These authors suggested that hyperplasia contributes to cardiomegaly when the individual fiber mass reaches a critical size. Linzbach[illegible] reported that the number of myocardial cells increased during severe concentric, pathological enlargement of the heart in man. In our nucleic acid studies, the hearts were enlarged 40 to 50 per cent. This enlargement may not have been severe enough for hyperplasia to play a dominant role. The contributions of invading inflammatory cells on the levels of cardiac nucleic acids in our studies, although indeterminable from these experiments, cannot be disregarded. (5) The decreased catecholamine concentrations (microgram per gram) but not the levels in each heart indicate that adrenergic innervation of the heart does not increase even though new tissue has been added. However similar results might have been obtained if edema contributed significantly to the enlargement or if the synthesis, uptake or detoxification of myocardial catecholamine were significantly altered. Studies with labelled precursors and labelled norepinephrine would help define the mechanism.

Several investigators feel that myocardial hypoxia is responsible for ISO-induced cardiac damage.[illegible] The data obtained in unanesthetized rats with chronic, indwelling aorta catheters (Fig. 3) may indirectly support this. ISO reduced systemic arterial blood pressure (possibly reducing coronary perfusion pressure) at a time when heart rate and myocardial oxygen demands were maximally elevated. This could result in repeated bouts of myocardial hypoxia which could induce lesions. Daniell and co-workers[illegible] have recently shown (in dogs) that when coronary blood flow was reduced to a critical level during ISO-induced hypotension the positive inotropic but not chronotropic actions of the drug were impaired. At this time cardiac metabolism seemed to shift from aerobic to anaerobic pathways. It cannot be determined from our studies whether the proposed hypoxia initiates cardiac hypertrophy in addition to the production of lesions, or whether the hypertrophy is strictly compensatory to the impaired function of injured areas of the ventricles. Some authors feel that persistent increases in the metabolic rate per heart beat or increased oxygen utilization of the heart may cause increased cardiac growth.[illegible]

Although many of the biochemical changes observed in ISO-induced *cardiomegaly* resemble those encountered with other forms of cardiac enlargement, the *mechanisms* responsible for the changes may be so complex and heterogeneous that it is a poor model for specifically studying cardiac hypertrophy. However this *ISO model* may provide valuable information about the chemical anatomy of the heart during the development of and recovery from infarctlike lesions. The model may be particularly valuable since it can be easily and quantitatively produced in small laboratory animals.

Summary

1 Isoproterenol (ISO) (5 mg per kilogram subcutaneously) induced maximal increases in the wet and dry weights of the four chambers of the rat heart when administered twice daily for 10 days. The degree of cardiomegaly was related to the duration of ISO treatment but was not greater in most instances, after 70 to 80 mg per kilogram than after 5 mg per kilogram. The size of the heart regressed when ISO treatment was discontinued. Propranolol antagonized the ISO response

2 The cardiomegaly induced by ISO was accompanied by microscopic evidence of infarctlike cardiac necrosis The severity of damage although not quantitated appeared to increase with the dosage of ISO or the duration of treatment

3 Total and extracellular cardiac water Na^+ Ca^{++} and Cl^- increased in relation to ISO dose. Heart K^+ increased after 1 or 5 mg per kilogram but decreased after 80 mg per kilogram of ISO administered twice daily for 2 days. Mg^{++} decreased to the same extent with all doses

4 The levels of cardiac protein RNA and DNA were augmented by ISO treatment with RNA increasing more than DNA. The incorporation of C^{14} labelled amino acids into the protein of the heart but not of the skeletal muscle, was enhanced by ISO

5 Catecholamine contents (microgram per gram) but not levels (microgram per heart) decreased as the size of the heart increased with ISO treatment

6 ISO (5 mg per kilogram) elicited prolonged tachycardia and hypotension in unanesthetized rats prepared with chronic, aortic catheters.

REFERENCES

1 Stanton, H. C and Schwartz, A. Effects of a hydrazine monoamine oxidase inhibitor (phenelzine) on isoproterenol-induced myocardiopathies in the rat, J Pharmacol. & Exper Therap 157:649 1967

2. Weeks, J R., and Jones, J A. Routine direct measurement of arterial pressure in unanesthetized rats, Proc. Soc. Exper Biol & Med. 104:646, 1960.

3 Hazelwood, C F Nichols, B L and Filers, W R. Theoretical computation of intracellular ion concentrations, Proceedings of Symposium on Biomedical Engineering 1:397 1966.

4 Munro, H. N and Fleck, A. The determination of nucleic acids, in Methods of biochemical analysis, Glick, David, editor New York, 1966, Interscience Publishers, Inc. vol. 14, page 113

5. Burton K. A study of the conditions and mechanism of the diphenylamine reaction for the colorimetric estimation of deoxyribonucleic acid, Biochem. J 62:315 1956.

6. Lowry O H Rosebrough, N J Farr A. L., and Randall, R. J Protein measurement with the Folin phenol reagent, J Biol. Chem. 193 265 1951

7 Anton, A. H., and Sayre, D F A study of the factors affecting the aluminum oxide trihydroxyindole procedure for the analysis of catecholamines, J Pharmacol. & Exper Therap. 138:360, 1962.

8 Stanton, H Estimation of grossly detectable isoproterenol induced myocardiopathies in rats using the rid t transformation, Toxic. Appl Pharmacol. 9:218, 1966.

9 Rona, G Chappel, C. I Balazs, T and Gaudry R. An infarct-like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat, Arch. Path. 67:443 1959

10. Lehr D Krukowski, M and Colon, R. Correlation of myocardial and renal necrosis with tissue electrolyte changes, J.A.M.A. 197:145, 1966.

11 Norman, T D The pathogenesis of cardiac hypertrophy Progr Cardiovas. Dis. 4:439 1962.

12 Meerson, F Z. A mechanism of hypertrophy and wear of the myocardium, Am. J Cardiol. 15 755 1965

13 Hoyle, T C. III Sumner R. G., and McIntosh, H D Nucleic acid and protein determinations in the study of experimental cardiomegaly J Lab & Clin. Med. 62:6 1963

14 Gluck, L. Talner N S. Stern, H., Gardner T H and Kulovich, M. V Experimental cardiac hypertrophy: Concentrations of RNA in the ventricles, Science 144 1244, 1964

15 Capers, T H : The relative amounts of DNA and concentrations of RNA in heart muscle of normal and hypertrophied hearts, Am Heart J 68 102, 1964.

16. Gudbjarnason S., DeSchryver C., Chiba, C. Yamanaka, J and Bing, R. J Protein and nucleic acid synthesis during the reparative process following myocardial infarction, Circulation Res. 15:320 1964.

17 Morimoto, S. Kishi, T Ito, Y and Kobayashi, T Nucleic acid metabolism in experimentally hypertrophied myocardium, Jap Heart J 6:443 1965

18. Tomita, K. Studies on myocardial protein metabolism in cardiac hypertrophy Jap Heart J 7:366, 1966.

19 Korecky B and French, I W : Nucleic acid synthesis in enlarged hearts of rats with nutritional anemia, Circulation Res. 21:641 1967

20 Stanton, H., and Brenner G. Adrenergic mechanism in submaxillary gland hypertrophy Fed. Proc. 27 709 1968.

21 Linzbach, A. J Heart failure from the point of view of quantitative anatomy Am. J Cardiol. 5:370, 1960.

22. Ferrans, V J Hibbs, R. G Black, W C. and Weilbaecher D G.: Isoproterenol-induced myocardial necrosis A histochemical and electron microscopic study Am. Heart J 68 71 1964

23 Handforth C. P Isoproterenol induced myocardial infarction in animals, Arch. Path 73 161 1962.

24. Daniell, H. B., Bagwell, E. E., and Walton, R. P : Limitation of myocardial function by reduced coronary blood flow during isoproterenol action, Circulation Res. 21:85, 1967

25. Bedeer H. S. The stim lus to hypertrophy of the myocardium, Circulation 30 128, 1964

The hemodynamic effects of paired pacing of the myocardium in reversible acute heart failure in the canine

David Thomas Kelly, M.B., Ch.B., M.R.A.C.P.
Cape Town, South Africa

Lopez and associates first described the use of paired pacing or selectively divided electrical stimuli to control heart rate in dogs. Since that time considerable interest in this technique has resulted in its successful use in the control of refractory arrhythmias.[1] Paired pacing also increases the force of cardiac contraction by postextrasystolic potentiation (PESP). Although this was described first in 1885 only recently has practical use been made of this phenomenon. When suitably spaced electrical stimuli of short duration are repetitively applied to the myocardium, 2 electrical depolarizations occur but only one discernable mechanical contraction—the first stimulus will cause contraction and the second occurring just after the absolute refractory period is mechanically ineffective. This property, a characteristic of mammalian cardiac muscle, causes PESP and thus results in a greatly enhanced force and velocity of contraction of the myocardium. Paired pacing has been shown not to cause an increase in output in the normal heart, but will cause marked improvement when heart failure is present.[4] The mechanism whereby contraction is increased although unknown is apparently not mediated through catecholamines.[7] The purpose of this report is to compare right atrial (RA) pacing with right ventricular paired pacing (RVpp) following autonomic blockade, during and after acute heart failure.

Method

Nine mongrel dogs weighing between 15 and 24 kilograms were studied. Each dog had previously undergone right thoracotomy under thiopentone anesthesia. The pericardium was opened and alcohol injected into the region of the sinus node which was also crushed to achieve sinus arrest. Pacemakers were sewn to the superior right atrium and to the anterior surface of the right ventricle. The dogs were allowed to recover and between 24 and 48 hours later were anesthetized with 15 mg. per kilogram of pentobarbitone and maintained with a constant infusion of approximately 0.05 mg. per kilogram per minute throughout the experiment. All dogs were intubated and breathed oxygen

From the Cardiac Clinic, Department of Medicine, Groote Schuur Hospital and the University of Cape Town, and the Cardiovascular-Pulmonary Research Group supported in the Department of Medicine by the Council for Scientific and Industrial Research.
Supported by a grant from the Cardiovascular-Pulmonary Research Group, Council for Scientific and Industrial Research.
Received for publication Jan. 26, 1968.
*Research Fellow, Cardiovascular-Pulmonary Research Group.

spontaneously through a Manley respirator. Catheters were placed in the left ventricle and thoracic aorta for recording pressures by a Statham P23D strain gauge. The first derivative of left ventricular pressure was recorded via the catheter on an R.C. differentiating circuit. These pressures plus the electrocardiogram were recorded photographically on a N.E.P. (Honeywell) recorder. Cardiac output was measured after an injection of 1.25 mg of cardio green into the right atrium by a constant volume syringe (Clay Adams Aupette) and sampling via a femoral artery using a Waters densitometer Model X302 with a Sanborn computer and constant withdrawal (38.9 c.c. per minute) Harvard pump. All blood was reinfused. The densitometer and computer were previously calibrated using the dog's blood with a preselected dye concentration. The heart was paced using a transistorized battery driven pulse generator capable of delivering single or paired electrical stimuli (Medtronics Inc. Model 583A). Throughout each experiment the rate was constant whether RA or RV paired pacing was used. The stimulus interval when paired pacing was used varied slightly for each dog but was in the range of 160 to 210 msec. Atropine 0.06 mg per kilogram and propranolol 0.4 mg per kilogram were given intravenously to each dog while the heart was being paced from the right atrium. After 5-minute dual outputs, left ventricular pressure plus its first derivative, left ventricular end-diastolic pressure, and aortic mean pressure were recorded. RVpp was begun and again after 4 minutes further records were taken. Following this RA pacing was restarted and further measurements taken to ensure that a steady state had persisted. When further control measurements had been taken a dose of propranolol up to 2.5 mg per kilogram was administered and angiotensin was infused intravenously at a constant rate of between 5 and 14 mcg per kilogram per minute depending on weight and response of the dog. Thus, by substantially increasing the afterload plus the large dose of propranolol, heart failure was produced as judged by a depressed cardiac output and raised end-diastolic pressure. RA pacing was compared to RVpp in the manner previously described. Angiotensin was discontinued and isoprenaline, at a rate of between 6 and 10 mcg per minute, was reinfused to overcome the beta blockade. When hemodynamics had returned to normal isoprenaline was discontinued half an hour later further measurements during RA and RVpp were taken. From the figures for cardiac output, systemic mean pressure left ventricular end-diastolic pressure and rate stroke volume and stroke work were calculated from the following formula

$$\text{Stroke work (Gm./M.)} = \frac{\text{SV (MAP} - \text{LVED)} \times 1.36}{100}$$

where SV stroke volume in c.c.s. MAP mean aortic pressure in mm. Hg LVED left ventricular end-diastolic pressure in mm Hg

The mean aortic pressure was measured by electrical integration

Results

Blood pressure, left ventricular end-diastolic pressure stroke volume and stroke work are shown in Table I during RAsp and RVpp. The rate is constant for each experiment but varied between 108 and 120. The control represents the findings after autonomic blockade, failure during heart failure and isoprenaline when heart failure had been reversed. Fig. 1 shows the changes noted in blood pressure with each type of pacing during

Table I

Type of pacing	*Aortic pressure*	*LVED pr*	*Stroke vol*	*Stroke work*
Control				
RA	97	3 3	19	28 5
RVpp	101	1 2	20	31 5
P values	>0.05	<0 001	>0 05	<0 05
Failure				
RA	141	10 1	17	79
RVpp	149	5 1	25	50
P values	<0.001	<0 001	<0.001	<0.001
Isoprenaline				
RA	93	3 6	32	28
RVpp	94	2 9	32	31
P values	>0.05	<0 001	>0 05	>0 05

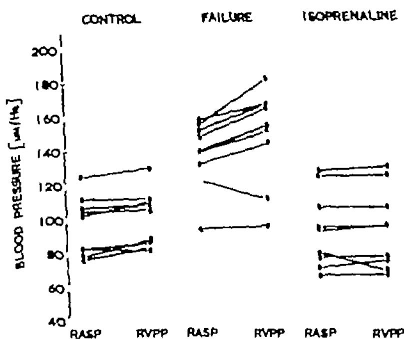


Fig. 1 The blood pressure in 9 dogs during control state, failure and after reversal by isoprenaline is compared during single pacing (RA p) and paired pacing (RV pp).

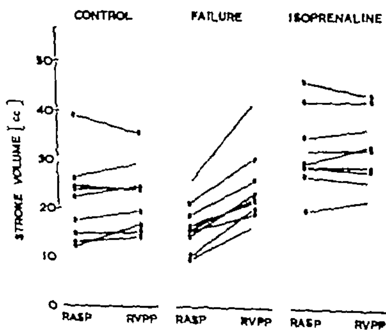


Fig. 2. Stroke volume is compared as in Fig. 1

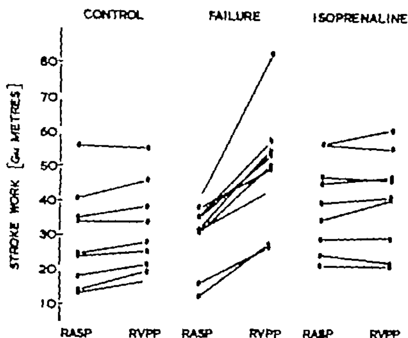


Fig. 3. Stroke work is compared as in Fig. 1

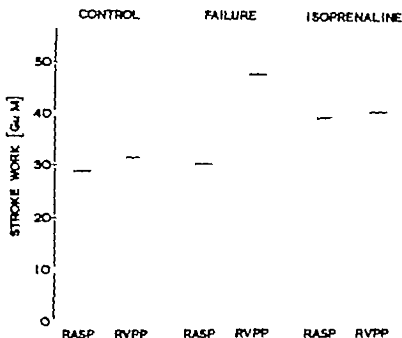


Fig. 4. Bar histograms showing the difference between single (*RAsp*) and paired pacing (*RVpp*) during heart failure and the similarity before and after reversal by isoprenaline.

control after isoprenaline when no significant change is seen and during failure when RVpp gives a higher pressure. The average change in blood pressure was 11 per cent during heart failure Fig 2 is set out on similar lines only stroke volume is illustrated and again the only changes noted are during heart failure (52 per cent) Fig 3 shows stroke work which incorporates both stroke volume and blood pressure and thus shows an even greater degree of change during heart failure of 66 per cent. The end-diastolic pressure decreased by an average of 110 per cent. Fig 4 also shows the marked difference between paired and single pacing in heart failure.

In all measurements during heart failure, the change between single and paired pacing was marked while during and after reversal by isoprenaline no great difference was found Fig 5 illustrates the 2 types of pacing and Fig 6 the change during heart failure.

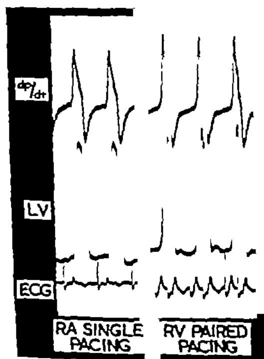


Fig 5 Showing right atrial single pacing (*ECG*) and the left ventricular pressure pulse (*LV*) and its rate of change of pressure (*dp/dt*) and right ventricular paired pacing with 2 electrical depolarizations and one significant mechanical contraction.

Discussion

When propranolol is given to produce beta-adrenergic blockade this may cause vagal overactivity with subsequent myocardial depression To avoid this, atropine was given in vagolytic dosage. Thus any autonomic nervous influence on the myocardium was blocked. This technique has been described and called pharmacological denervation.[8]

The cardiac output in anesthetized dogs is known to fluctuate especially with barbiturate anesthesia. Part of this variation is thought to be due to increased sympathetic tone and thus beta adrenergic blockade will tend to overcome this. As barbiturates may cause significant myocardial depression light anesthesia was used and a continuous infusion given to maintain this state

The sinus node was destroyed because with the slower rhythm paired pacing could be established at the same rate as single pacing and RA pacing could be satisfactorily achieved without sinus node interference.

When stroke work is used as an index of myocardial function the rate must be constant otherwise the spontaneous fluctuation found in an anesthetized dog will cause a very significant change in stroke volume due to rate alone, and invalidate comparisons which should depend on output changes Accordingly the rate was constant throughout each experiment.

Angiotensin was used to increase the afterload and provide significant ventricular stress. The drug is suitable because it is short acting and has no significant tachyphylaxis during an acute experiment. While there is some inotropic action in the papillary muscle preparation[12] when the cardiovascular system is intact there is no significant myocardial or venous action. In combination with the larger dose of propranolol acute heart failure could be precipitated After total autonomic blockade paired pacing produced little external improvement in the function of the heart muscle as a pump. Although the end diastolic pressure and the dp/dt of the left ventricular pulse were markedly altered stroke volume and blood pressure remained essentially unchanged and stroke work only marginally increased thus show

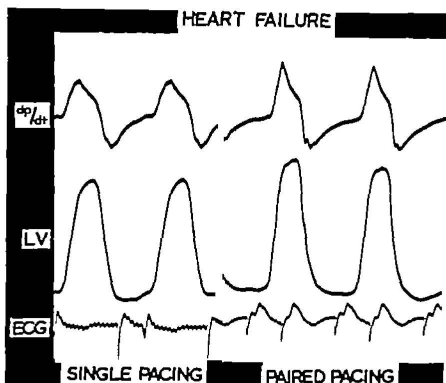


Fig. 6. Illustrating the change in left ventricular pressure (*LV*) and its rate of change of pressure between single and paired pacing during heart failure.

ing that the powerful inotropic stimulus of paired pacing when there is no significant myocardial depression present serves no useful purpose. The natural homeostatic mechanism[11] which controls the rapid reflex adjustments for optimal pressures and flows in the circulation reduces the tendency of a powerful inotropic stimulus, like paired pacing to alter circulatory hemodynamics. When, however, acute heart failure is induced, the difference between paired and single pacing is very striking and in other experiments the survival of the dog depended upon continual application of paired pacing. Thus, in the decompensated heart this powerful inotropic stimulus may restore or tends to restore the circulation toward normal. When the excess afterload was removed by stopping angiotensin and the effect of propranolol was reversed by isoprenaline infusion, the hemodynamics returned to normal and in this situation no significant difference was found between paired and single pacing, as was seen before heart failure had been produced. Paired electrical stimulation with PESP is thus a powerful aid to the therapy of acute heart failure and may be used in conjunction with other inotropic agents as its action is independent. This use of paired pacing has been well documented in laboratory animals with right heart failure.

Apart from the change in end-diastolic pressure and dp/dt due to change in compliance and velocity of contraction, both known effects of paired pacing, the hemodynamic state is not improved in the normal as has been shown by several workers.

The use of paired pacing may be compared to the effects of the digitalis glycosides on cardiac muscle. Digoxin in the normal compensated circulatory state causes no improvement[7] but in failure tends to restore the deranged circulation. Both paired pacing and digoxin alter the force velocity curve in the normal but the oxygen consumption is increased only

with paired pacing presumably reflecting a greater velocity of contraction.[13] When paired pacing is compared with another powerful inotropic stimulus such as isoprenaline, considerable differences are noted as isoprenaline will increase output in the normal;[1] this reflects the manifold capacity of the drug to alter the peripheral regulatory mechanisms rather than the single inotropic action on myocardial muscle.

Electrical stimulation of heart muscle releases the local stores of adrenergic compounds.[17] The effects of this may be decreased if small electrodes, a lower frequency of stimulation and energy just above the threshold is used. However the frequency of stimulation is high and thus stimulation alone could have had an inotropic effect. As the propranolol was given in dosage sufficient to block beta adrenergic receptors, the effect of paired pacing is obviously not mediated through catecholamines. Braunwald and co-workers[18] have shown that paired pacing is effective both in the reserpinized heart and after beta adrenergic blockade.

Propranolol is known to reduce resting hemodynamics. This is due to 2 factors: first, removal of the adrenergic stimulus to the myocardium which varies considerably depending on excitatory factors and in the anesthetized dog thought to be significant.

The second postulated mechanism is a separate myocardial depressant action analogous to quinidine.[9] In the initial dosage given, this is unimportant and the reduction in stroke work is due to the beta blockade alone as when compared with another beta-blocking agent without further depressant effects, no differences was shown.[20] When large doses are given, however, this factor becomes important as heart failure which is not precipitated by increased afterload alone is produced.

The powerful inotropic stimulus of paired pacing in most dogs, however, did not improve the circulatory state showing that the reduction produced by beta blockade is not significant or that the methods of measurements are too crude for such a distinction. When obvious heart failure was produced only then does paired pacing result in a significant improvement in the hemodynamic state.

Summary

RA and RVpp were compared in 9 anesthetized dogs. All animals had previously been given atropine and propranolol in dosage sufficient to cause blockade of the autonomic nervous system. No marked difference was found between the 2 types of pacing but when acute heart failure was induced paired pacing significantly increased the output pressure and stroke work of the heart.

The left ventricular end-diastolic pressure decreased markedly and dp/dt increased. Paired pacing tends to return the decompensated heart to normality and is a powerful inotropic stimulus. When heart failure was reversed by decreasing the afterload and overcoming beta blockade with isoprenaline the 2 types of pacing gave the same hemodynamic result.

Paired pacing is not mediated through the adrenergic system and is an additional therapeutic weapon for the treatment of heart failure.

I wish to thank Professor V. Schrire and Professor C. N. Barnard for their help and encouragement and Miss E. E. Firth for her technical assistance.

I am most grateful for the financial assistance received from the Council for Scientific and Industrial Research.

This work was done during the tenureship of C.S.I.R. Senior Research Officer post in the Cardiovascular Pulmonary Research Group.

REFERENCES

1. Lopez, J. F., Edelist, A., and Katz, L. N.: Slowing of the heart rate by artificial electrical stimuli with pulses of long duration in the dog, Circulation 28:759, 1963.
2. Langendorf, R., and Pick, A.: Observations on the clinical use of paired electrical stimulation of the heart, Bull. New York Acad. Med. 41:535, 1965.
3. Cranefield, P. F.: The force of contraction of extrasystoles and the potentiation of force of the postextrasystolic contraction: A historical review, Bull. New York Acad. Med. 41:419, 1965.
4. Sonnenblick, E. H., Frommer, P. L., and Braunwald, E.: Electroaugmentation of human and cat papillary muscle produced by paired electrical stimulation, Bull. New York Acad. Med. 41:554, 1965.
5. Goetz, R. H., Jallah, E. M., and Goetz, V. M.: Circulatory dynamics of paired pacing in hypovolemic and cardiogenic shock, Am. Heart J. 73:506, 1967.
6. Hoffman, B. F., Bartelstone, H. J., Scherlag, B. J., and Cranefield, P. F.: Effects of postextrasystolic potentiation on normal and failing

hearts, Bull. New York Acad. Med. 41:498, 1965
7. Braunwald, E., Ross, J. J. Frommer P. L., Williams, J. F. J. Sonnenblick, E. H. and Gault, J. H. Clinical observations on paired electrical stimulation of the heart. Effects on ventricular performance and heart rate, Am. J. Med. 37 700, 1964
8. Stephen, S. A. Unwanted effects of Propranolol Am. J. Cardiol. 18:463 1966.
9. Jose, A. D : Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man, Am. J. Cardiol. 18:476, 1966.
10. Shabetai, R., Fowler N. O and Hurlburt O. Hemodynamic studies of dogs under pentobarbital and morphine chloralose anesthesia J. Surg. Res. 3:263 1963
11. Fowler N. O. and Holmes, J. C. Coronary and myocardial actions of angiotensin, Circulation Res. 14 191, 1964
12. Koch-Weser J. The nature of the inotropic action of angiotensin on the ventricular myocardium, Circulation Res. 16:230, 1966.
13. Sarnoff S. J. Mitchell, J. H., Gilmore, J. P. and Remensnyder J. P. Homeometric autoregulation in the heart, Circulation Res. 8 1077 1960.
14. Bartelstone, H. J. Scherlag, B. J. Hoffman, B. F. and Cranefield, P. F. Demonstration of variable diastolic compliance associated with paired stimulation of the dog heart, Bull. New York Acad. Med. 41:616, 1965
15. Sonnenblick, E. H. Ross, J. Covell, J. W. Kaiser G. A., and Braunwald, E. Velocity of contraction as a determinant of myocardial oxygen consumption, Am. J. Physiol. 209:919, 1965
16. Krasnow N. Rolett, E. L. Yurchak, P. M. Hood W. B. and Gorlin, R.: Isoproterenol and cardiovascular performance, Am. J. Med. 37:514 1964
17. Blinks, J. R., and Koch-Weser J.: Physical factors in the analysis of the actions of drugs on myocardial contractility. Pharmacol. Rev. 15:531 1963
18. Braunwald, E., Bloodwell, R. D. Goldberg, L. I., and Morrow A. G. Studies on digitalis. IV. Observations in man on the effects of digitalis preparations on the contractility of the non-failing heart and on total vascular resistance, J. Clin. Invest. 40:52, 1961
19. Levy J. V. and Richards, V. Inotropic and metabolic effects of three beta-adrenergic receptor blocking drugs on isolated rabbit left atria, J. Pharmacol. & Exper. Therap. 150:361 1965.
20. Kelly D. T. Unpublished observations.

Symptomatic constrictive pericarditis developing 45 years after radiation therapy to the mediastinum

A review of radiation pericarditis

*John M Haas Major MC USA**
Denver Colo

The etiology of constrictive pericarditis remains in doubt in many patients. The incidence of tuberculous pericarditis and chronic constrictive pericarditis is decreasing and being replaced by such entities as acute nonspecific pericarditis with chronic constriction [2] histoplasmosis,[3,4] rarely chronic rheumatic valvular heart disease [5] rheumatoid disease, [7] disseminated lupus erythematosus,[8] infectious mononucleosis, as well as trauma [9-11] and suppurative infections of the pericardium.[1] Cases have now been reported of acute pericarditis developing during or shortly following radiotherapy to the thorax, usually for malignant neoplasms of the breast and mediastinum. Chronic constrictive pericarditis has subsequently developed 1 to 20 years later.

The following case is thought to represent symptomatic constrictive pericarditis, developing 45 years after radiation to the chest as a child.

Case report

C. M. was a 54-year-old Caucasian woman, gravida I para I who began experiencing menopausal symptoms in 1963. After 18 months of no vaginal bleeding the patient developed menstrual irregularity with spotting. A cervical dilatation and curettage was performed at Martin Army Hospital, Ft. Benning Ga., and a diagnosis of adenoacanthoma of the endometrium was made. The patient was transferred to Walter Reed General Hospital in February 1965 for radiation therapy.

Her past history revealed that she had smoked ½ pack of cigarettes daily for 15 to 20 years, consumed no alcoholic beverages, and was taking Orinase one tablet twice daily for a diagnosis (made in 1960), of maturity-onset type diabetes mellitus. The patient father died at age 37 of tuberculosis and her mother of heart disease at age 60. The patient had had poorly documented rheumatic fever at 7 years of age. At the age of 9 the patient had had radiation therapy to the chest for something she thought related to her thymus and developed symptoms compatible with severe radiation sickness thereafter. No other details are known. Approximately 10 to 12 years ago, the patient was placed on digitalis and diuretics because of mild dyspnea on exertion, nonexertional chest pain, and occasional swelling of the lower extremities. In December 1960 a diagnosis of arteriosclerotic heart disease was made on the basis of a complete right bundle branch block (RBBB) noted on her electrocardiogram (ECG).

The physical examination at the time of admission to Walter Reed General Hospital revealed blood pressure of 106/84, pulse 76 and regular, weight 112 pounds, and height 4 feet 11 inches. The pertinent findings included a markedly hypoplastic thorax with hyperpigmentation and telangi-

From the Division of Cardiology Fitzsimons General Hospital.
This material has been reviewed by the Office of The Surgeon General, Department of the Army and there is no objection to its presentation and/or publication. This review does not imply any endorsement of the opinions advanced or any recommendation of such products as may be named.
Received for publication Nov 22, 1967
*Resident in Cardiology Fitzsimons General Hospital.

*Table I Cardiac catheterization data**

Date	*IVC*	*RA*	*RV*	*PA*	*PAW*	*BA*
March 1 1965		A = 13/6 (9)	31/5-12*	28/11 (19)	16/10 (12)	
Dec. 14 1965	(18-19)	A = 23 V = 20/(18-19)	37-42/10-25†	37-42/20 (25-28)	A = 20-25 V = 16-25 (17 21)	120-140/70-75 (90)

Figures in parentheses signify mean pressures.
*All pressures expressed in millimeters of mercury.
†Signifies end-diastolic pressures.

ectasia of the skin which was atrophic and relatively fixed to the rib cage. There was a total lack of breast development and the over-all appearance of the chest resembled that of 10-year-old child. The lungs were clear to auscultation and percussion though there were restricted excursions of the chest wall. The apical impulse was in the fifth intercostal space, 2 cm. lateral to the midclavicular line. The heart tones were of good quality with an intermittent third heart sound at the apex. The pulmonic second sound split physiologically. There was a Grade III/VI ejection-type systolic murmur at the apex. A faint friction rub was noted for the first time. The liver was palpable 5 cm. below the right costal margin and ++ pitting edema of the feet was noted. A venous pressure was 11 cm of water and the circulation time was 14 seconds.

The pertinent laboratory data revealed normal white cell count and differential, hemoglobin and hematocrit, and urinalysis. The sedimentation rate was elevated to 30 mm. The blood urea nitrogen (BUN) and serum electrolytes were normal. Liver function studies were normal at this time. A fasting and two-hour postprandial blood sugar were 108 mg and 241 mg respectively. The serum cholesterol was 472 mg. Cardiac fluoroscopy was reported as normal. Scout films of the abdomen revealed hepatomegaly unchanged from films dating to 1954 and thought to represent displacement of the liver out of the hypoplastic thorax. Pulmonary function studies were performed and showed moderate restriction of all lung compartments. The patient underwent cardiac catheterization in March, 1965 (Table I).

The following diagnoses were made fibrous pericarditis without significant restriction, pulmonary fibrosis without significant pulmonary hypertension, probable arteriosclerotic heart disease, and diabetes mellitus.

The patient was seen by the Urology Department, and a large extrinsic mass was noted pressing centrally in the posterosuperior portion of the bladder with bilateral elevation of the ureters. In May 1965 the patient was treated with 80 mg of radium in an Ernst applicator to the uterus as well as receiving 4,800 externally the latter divided over 36 doses. Except for mild radiation proctitis, the patient tolerated the radiotherapy well.

The patient was discharged from the hospital and did well until August, 1965 when she began to develop intermittent abdominal cramps, swelling, and distention of the abdomen with increasing weakness and shortness of breath. She also noted some orthopnea, cough, and swelling of the ankles. When seen on Nov. 29 1965 the patient appeared chronically ill. Her blood pressure was 110/70 with 20 mm. pulsus paradoxicus. The pulse was 100 and regular. The patient preferred sitting up at 75 degrees for comfort. The neck veins were distended at 45 degrees with prominent A waves. There were râles in both lung bases. The apical impulse was not palpable and the heart sounds were diminished in intensity. A friction rub was again noted. A loud third heart sound was heard at the apex. The liver was now palpable 8 cm below the right costal margin associated with obvious ascites, and +++ pitting edema of lower extremities and sacral region.

The admission roentgenogram of the chest was essentially unchanged but on December 6 pleural effusion and increased pulmonary vascular markings were noted (Fig. 1). The ECG showed loss of voltage from the previous tracings (Fig. 2). The venous pressure was 27 cm. of water.

The patient was digitalized and diuretics were administered, but there was no improvement. She was transferred to the Walter Reed General Hospital with a diagnosis of constrictive pericarditis. Additional studies performed at the time of this admission revealed a negative intermediate strength purified-protein derivative skin test but faintly reactive 2d-strength reaction, normal white cell count, hemoglobin and hematocrit, and urinalysis. The sedimentation rate was 40 mm. Excretory urograms, liver scan, and an inferior vena cavagram were all normal. The ECG were unchanged. The chest roentgenogram showed no further change. Cardiac fluoroscopy was repeated and minimal pericardial calcification was noted. The BUN and serum electrolytes were normal. A liver function study was again within normal limits with the exception of the alkaline phosphatase of 15.7 KA units. Repeat pulmonary function studies again showed moderate restriction of all lung compartments but with no change from February 1965. On Dec. 14 1965 cardiac catheterization was again performed and revealed findings consistent with chronic constrictive pericarditis (Table I). On Jan. 12 1966, bilateral anterior thoracotomy was performed and marked thickening of the pericardium with minimal calcification noted. The peri



Fig. 1. A, The chest roentgenogram taken in 1954, the oldest film available, shows a cardiac silhouette of normal size and configuration. *B*, The chest roentgenogram taken in December, 1965, shows cardiomegaly and haziness of the right costophrenic angle. *C*, The lateral roentgenogram of the chest is shown to demonstrate the relatively small size of the chest and absent breast shadows secondary to radiation as a child.

cardium was resected and showed only nonspecific fibrosis with negative smears, cultures, and special tissue stains for mycobacterium tuberculosis, fungi, and bacteria. *Postoperatively*, a brisk diuresis ensued amounting to 2,500 ml. in the first 13 hours. On Jan. 13, the patient became hypotensive with a fall in her urinary output from 50 to 10 ml. per hour. Aramine, Isuprel, whole blood, and fluids were administered and it was possible to discontinue the pressor agents on January 16. Her progress thereafter was satisfactory with ambulation on January 19. The patient lost 8 pounds with clearing of her ascites and edema while continuing on digoxin and Oretic.

On April 13, 1966, the patient was readmitted to Walter Reed General Hospital because of difficulty with healing of the thoracotomy incision, specifically for an ulcer of the chest wall, and an attempt at skin grafting. At this time, her blood pressure was 110/60 with no pulsus paradoxicus. There was no neck vein distention or edema, but the liver was still palpable 2 to 3 cm. below the right costal margin. The lungs were clear. Examination of the heart revealed a normal sinus rhythm and good heart tones without the previously described friction rub or third heart sound. The ejection-type systolic murmur persisted. The patient, over all, looked extremely well, and her exercise tolerance had *improved markedly*.

Discussion

Acute pericarditis following irradiation to the mediastinum for teratoma, seminomas, thymomas, and lymphomas, and to the left chest region for adenocarcinoma of the breast, has been described occurring during or shortly after radiation therapy. Constrictive pericarditis has been infrequently reported occurring 1 to 20 years postradiation.[13-18]

*The patient was treated with an un-*known quantity of radiation to the mediastinum for specifically unknown reasons at the age of 9 with subsequent arrest of growth in the structures in the chest wall, rib cage, and breasts with secondary radiation changes to the skin. There was no interval history of chest trauma or illnesses to arouse suspicion of acute pericarditis at any time, and her preoperative as well as postoperative studies with tissue and fluid cultures of the pericardium as well as histological examination of the pericardium failed to demonstrate another possible etiological agent. We, therefore, presume that this patient developed fibrous pericarditis secondary to radiation therapy. *What precipitated clinically* symptomatic constrictive pericarditis 45 years after

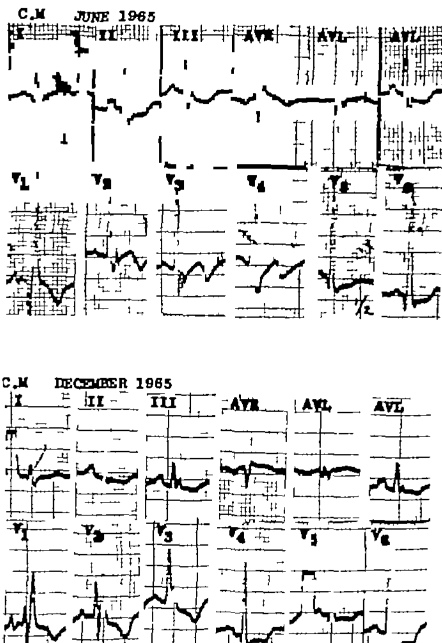


Fig. 2. The ECG of June, 1965 shows complete RBBB with secondary ST T wave changes. The prominent voltage probably reflects close proximity of the precordial electrodes to the heart. The ECG in December 1965, shows a sinus tachycardia and loss of voltage when compared to the previous tracing.

radiation therapy in this case and in other cases reported in literature can only be speculated upon.

The subject of pleural reaction and pneumonitis following radiation therapy with subsequent pulmonary fibrosis appears to be well established[11] but the controversy of the effects of radiation on the pericardium and myocardium per se still exists with conflicting experimental and clinical studies. In 1932 Desjardins[2] concluded that the specific radiosensitivity of the heart was definitely less in comparison with other organs, and that ordinary

doses of radiation exerted no injurious effects. Extremely high doses were necessary to produce direct degenerative changes to the myocardium. Leach and Sugiura,[illegible] in studying the effects of high voltage roentgen rays on the hearts of adult rats, administered progressively increasing doses from 1,500 to 20 000 r using 200 kv a 0.5 mm copper filter through a 0 5 to 1.5 cm. precordial window and found the critical dose to the myocardium to be approximately 10 000 r At this dosage, capillary hemorrhage, round-cell infiltration, myocardial degeneration and necrosis occurred The pericardium withstood doses of 20,000 r In a second study employing the same methods and doses, he found no late effects on the heart with doses of 7,500 r in a 2 to 14 month follow up.[illegible] Leach[illegible] also studied 85 patients categorized into three groups Class I radiation to the head neck rectum, and genital tract Class II lymphoma and teratoma with generalized radiation including the thorax Class III carcinoma of the breast lung esophagus and cardia of the stomach. It was concluded from this study that there was no evidence that radiation per se caused injury to the heart. Minor T wave changes occurred in all groups but were nonspecific in etiology and were attributed to such things as fever anemia, toxemia, or positional changes of the heart within the thorax due to a mediastinal shift or elevated diaphragm. Three patients in Class III developed chronic pericarditis and pleuropericardial adhesions, but these were attributed to infections of the thoracic wall ribs, and lungs with extension to the pericardium by continuity Leucutia[illegible] also concluded from review of the literature at that time, that no damage was incurred by the heart per se by the various modes of radiation that were currently being employed. Jones and Wedgewood[27] on reviewing 99 cases of esophageal carcinoma receiving 1 mv roentgenogram therapy with doses of 5 to 6,000 r over 30 to 42 days, noted no pathological evidence of radiation carditis. Studying 26 consecutive patients for carcinoma of the breast, he noted that in the thin-chested patient with a left radical mastectomy as much as 3,000 r are delivered to the anterior heart wall over 28 days, with the least radiation 1,500 r in those patients with carcinoma of the right breast unoperated. In a 2 year follow-up no clinical or roentgenographic evidence of pathological changes were noted and the transient T wave changes in the right precordial leads were attributed to variation of electrode position. Four cases showing serial electrocardiographic abnormalities 4 to 63 weeks after radiation occurred in patients with evidence of ischemic heart disease, but a localized pericardial reaction could not be excluded Catteral[illegible] investigating the same area, studied the effects of radiation on the heart in 26 patients with carcinoma of the carina of the trachea and breast. Six patients with carcinoma of the carina received 4 000 r fractioned daily over 1 month from a telecobalt 60 unit to anterior and posterior portals and found no clinical or electrocardiographic evidence of pericarditis. Eight patients with carcinoma of the right breast and 12 patients with carcinoma of the left breast received 3,650 r 10 fractionated doses every other day over 3 weeks, using 250 kv with an estimated dose of 3,000 r to the internal mammary chain and a calculated dose of 1,000 r to the heart. A total of 35 per cent of the patients with carcinoma of the left breast developed T wave changes immediately after treatment or as late as 4 months. These resolved by 1 year on follow up and again were not considered typical of epicarditis with no clinical symptoms accompanying these changes Other investigators[illegible] have done similar research and have noted transient T wave changes which they regarded as of no clinical significance and which were reversible therefore it was concluded that these changes did not reflect myocardial injury Conversely Whitfield and Kunker[illegible] and more recently Cooper[illegible] studying mega voltage radiation to the left side of the chest for carcinoma of the breast, have regarded the T wave changes as representing myocardial damage. No conclusive enzyme changes, alteration of heart size, or the appearance of clinical symptoms or signs appeared In 1960 Jones and Wedgewood,[27] on reviewing the subject of the effects of radiation of the heart, concluded that structural changes in the heart occurred only after very high radiation doses

and that the only direct evidence of damage to the pericardium were again associated with very high single or protracted dosage, basing these conclusions on the aforementioned clinical studies and the experimental work of Leach in rats.

In 1945 Blumenfeld and Thomas[18] described a case of pericardial effusion of 4½ years duration following a single massive dose of radiation through an open mastectomy wound for carcinoma of the breast. The total calculated dose to the pericardium was 8 250 tissue r Autopsy revealed gross pericardial thickening and histologically dense hyalinized fibrous tissue in the parietal and visceral layers with large discrete fibroblasts having large bizarre, somewhat irregularly deeply staining nuclei. The myocardium showed widespread focal fibrosis, most marked in the area or direction of radiation. Some coronary artery intimal proliferation were also noted These changes corresponded with the anatomical and histological findings in experimental animals.[23]

In 1940 Freid and Goldberg[22] described a case in which pericardial effusion developed 6 months after radiation for carcinoma of the left breast, and found four instances of pericarditis with effusion at autopsy in eight patients with radiation pneumonitis. Leach[23] as previously mentioned noted three patients with pericarditis and pleuropericardial adhesions who had received large doses of radiation but attributed these findings to extension of the inflammatory and infectious processes occurring in the chest wall and lung Connally and Burchell[5] in their 10 year survey of pericarditis, reported 8 cases of acute radiation pericarditis following radiation to the mediastinum and the thoracic region one patient developing two distinct episodes, each following courses of radiation therapy separated by 2 month intervals Two patients developed constrictive pericarditis years later Recently Cohn and colleagues have described 20 cases receiving at least 4 000 r to the area of the heart in the treatment of various malignant neoplasms, including 12 patients with acute pericarditis 9 of whom had effusion and 5 tamponade 6 patients with chronic pericardial effusion and 8 patients with chronic constrictive pericarditis and endomyocardial fibrosis. Williams[28] regarded mediastinal and pericardial reactions as uncommon—but important—complications of radiation therapy when employing supervoltage roentgenogram doses of 4 000 r over a 30 day period Three cases of overt pericarditis occurred on therapy and one case of constrictive pericarditis developed one year later Hurst,[8] Gimlette,[17] and Steinberg[9] have all reported cases of chronic constrictive pericarditis developing 1 to 20 years after radiation Slater and associates[19] reported a case of constrictive pericarditis developing 14 years following left radical mastectomy and radiation therapy At autopsy scattered tumor cells were found in the thickened pericardium as a residual of the previously treated carcinoma of the breast.

Jones and Wedgewood[17] like Williams, concluded (1) that such mediastinopericardial reactions are conditioned by the response of a sensitive neoplastic or inflammatory process which lies on or involves the pericardium and speculated that in the case of Slater and co-workers[19] and others that the response might be mainly due to a scirrhous stromal reaction to tumor cells, and the role played by radiation an ancillary one (2) that such syndromes, while of clinical importance do not provide evidence of the inherent radiation reactivity or tolerance of the normal pericardium

Until such time as sufficient tissue has been examined histologically at the moment of initial electrocardiography changes, the problem of subclinical pericarditis, its pathogenesis, and its correlation with electrocardiographic changes will continue.

Summary

Though the exact mechanism of radiation pericarditis has not been resolved and controversy still exists among the various medical disciplines sufficient cases have now been reported to justify its classification as a clinical entity

This report describes a case of chronic constrictive pericarditis with the unusual feature of becoming symptomatic 45 years after radiation therapy to the mediastinum as a child the longest latent period that has as yet been reported in the literature.

REFERENCES

1. Gibbons, J. E., Goldbloom, R. B., and Dobell, A. R. C.: Rapidly developing pericardial constriction in children following acute nonspecific pericarditis, Am. J. Cardiol. 15:863, 1965.
2. Azar, G. J.: Acute nonspecific pericarditis complicated by the development of constrictive pericarditis, Am. Heart J. 65:414, 1963.
3. Rosenbaum, A. E., Schweppe, H. I., and Rubin, E. R.: Constrictive pericarditis, pneumopericardium and aortic aneurysm due to histoplasma capsulatum, New England J. Med. 270:935, 1964.
4. Wooley, C. F., and Hosier, D. M.: Constrictive pericarditis due to histoplasma capsulatum, New England J. Med. 264:1230, 1961.
5. Connolly, D. C., and Burchell, H. B.: Pericarditis: 10 year survey, Am. J. Cardiol. 7:7, 1961.
6. Tubbs, O. S., Slade, P. R. H., and Turner Warwick, M.: Constrictive pericarditis in association with rheumatoid arthritis, Thorax 19:555, 1964.
7. Keith, T. A., III: Chronic constrictive pericarditis in association with rheumatoid arthritis, Circulation 25:477, 1962.
8. Yurchak, P. M.: Constrictive pericarditis complicating disseminated lupus erythematosis, Circulation 31:113, 1965.
9. Wilson, D. R., Leukel, S. C., and Peterson, J. F.: Acute constrictive epicarditis following infectious mononucleosis, Circulation 23:257, 1961.
10. Goldstein, S.: Diagnosis of adhesive constrictive pericarditis, Am. Heart J. 68:576, 1964.
11. McKusick, V. A., Kay, J. H., and Isaac, J. P.: Constrictive pericarditis following traumatic hemopericardium, Ann. Surg. 142:97, 1955.
12. Schaffer, A. I.: A case of traumatic pericarditis with chronic tamponade and constriction, Am. J. Cardiol. 7:125, 1961.
13. Mortensen, V., and Warburg, E.: Chronic constrictive pericarditis, Acta med. scandinav. 131:203, 1948.
14. Sellors, T. H.: Constrictive pericarditis, Brit. J. Surg. 33:215, 1946.
15. Slater, S. R., Kroop, I. G., and Zuckerman, S.: Constrictive pericarditis caused by solitary metastatic carcinoma of the pericardium and complicated by radiation fibrosis of the mediastinum, Am. Heart J. 43:401, 1952.
16. Blumenfeld, H., and Thomas, S. F.: Chronic massive pericardial effusion following roentgen therapy for carcinoma of the breast with case report, Radiology 44:335, 1945.
17. Gimlette, T. M. D.: Constrictive pericarditis, Brit. Heart J. 21:9, 1959.
18. Steinberg, I.: Effusive-constrictive radiation pericarditis, two cases illustrating value of angiocardiography in diagnosis, Am. J. Cardiol. 19:434, 1967.
19. Cohn, K. F., Steward, J. R., and Hancock, W. E.: Heart and pericardial disease due to radiation, Circulation (Suppl. 3) 34:76, 1966 (abstr.)
20. Hurst, D. W.: Radiation fibrosis of the pericardium with cardiac tamponade, Canad. M. A. J. 81:377, 1959.
21. Leach, J. E., Farrow, J. H., Foote, F. W., Jr., and Wawro, N. W.: Fibrosis of the lung following roentgen radiation for carcinoma of the breast, Am. J. Roentgenol. 47:740, 1942.
22. Desjardins, A. U.: Action of roentgenrays and radium on the heart and lungs, Am. J. Roentgenol. 27:149, 1932.
23. Leach, J. E., and Sugiura, K.: Effect of high voltage roentgen rays on the heart of adult rats, Am. J. Roentgenol. 45:414, 1941.
24. Leach, J. E.: Late effect of high voltage roentgen rays on the heart of adult rats, Am. J. Roentgenol. 48:81, 1942.
25. Leach, J. F.: Effect of roentgen therapy on the heart, a clinical study, Arch. Int. Med. 72:715, 1943.
26. Lenarduzzi?, T.: Effect of roentgen therapy on the heart, Editorial, Am. J. Roentgenol. 51:379, 1944.
27. Jones, A., and Wedgewood, J.: Effects of radiation on the heart, Brit. J. Radiol. 33:138, 1960.
28. Catterall, M.: Effect of radiation upon the heart, Brit. J. Radiol. 33:159, 1960.
29. Emery, E. S., and Gordon, B.: Effect of roentgenotherapy on the human heart, Am. J. M. Sc. 170:884, 1925.
30. Rubin, P., Andrews, J. R., Poulton, R., and Flick, A.: Response of radiation pneumonitis to adrenocorticoids, Am. J. Roentgenol. 79:453, 1958.
31. Whitfield, A. G. W., and Kunkler, P. B.: Radiation reactions in the heart, Brit. Heart J. 19:53, 1957.
32. Cooper, E. E.: Radiation damage to the myocardium during therapy for breast cancer, Circulation (Suppl. 3) 34:78, 1966 (abstr.)
33. Davis, K. S.: Intrathoracic changes following x-ray treatment: clinical and experimental study, Radiology 3:301, 1924.
34. Freid, J. R., and Goldberg, J. R.: Post irradiation changes in the lungs and heart, Am. J. Roentgenol. 43:877, 1940.
35. Williams, L. G.: Thymic tumours associated with myasthenia gravis with special reference to the effects of x-ray therapy, J. Fac. Radiol. 3:176, 1952.

Marfan's syndrome and mitral valve disease
Acute surgical emergencies

*James W Simpson M.D **
*James J Nora M.D ***
*Dan G McNamara M.D ****
Houston Texas

It is well known that patients with Marfan's syndrome may present as cardiovascular surgical emergencies because of dissecting aortic aneurysm[1] The purpose of this report is to call attention to the occurrence of acute surgical emergencies involving the mitral valve due to rupture of chordae tendineae.

Case report

A 4-year-old Caucasian girl was referred to Texas Children Hospital on Sept. 12, 1966 for evaluation of a heart murmur and symptoms of congestive heart failure.

The past history indicated that she had been normal at birth although the attending pediatrician described her appearance in the newborn period as "long, thin, and boney simulating her mother characteristics. A heart murmur was heard for the first time when she was 9 months old.

The patient mother is 32 years of age and has classic features of Marfan syndrome with long slender arms, legs, fingers and toes, kyphoscoliosis, *pectus excavatum* dislocation of the lens of each eye, a high-arched palate, and a mitral insufficiency murmur No other members of the family have obvious stigmata of Marfan's syndrome. The parents have had no other children.

Upon examination, the patient was found to be a tall, slender child with marked kyphoscoliosis, wearing thick-lensed eyeglasses. There was marked pectus excavatum deformity of the chest (Fig 1). Hyperextensibilities of fingers and toes was demonstrated. Her height was 102 cm her arm span was 103 cm., pubis to ground measurement was 52 cm., and the head to pubis measurement was 50 cm. Her weight was 28½ pounds. The heart rate was 120 per minute and regular The respiratory rate was 32 per minute. The blood pressure in her arms was 90/60 mm. Hg and the leg blood pressure was 98/65 mm. Hg

Eye examination revealed her to be myopic, but there was no dislocation of the lens and the retina appeared normal She had a high-arched palate. Her lungs were clear

Examination of the cardiovascular system revealed normal peripheral pulses. There was distention of the neck veins. The apical impulse was forceful and diffusely palpable in the fifth and sixth left intercostal spaces at the midaxillary line. A Grade IV/VI regurgitant type, high-pitched, systolic murmur was heard at the apex which radiated laterally to the back. It was followed by Grade II/VI low-pitched rumbling mid-diastolic murmur

There was small umbilical herniation. There was no enlargement of the liver or spleen and no edema, cyanosis, or clubbing could be detected.

The electrocardiogram (ECG) showed sinus rhythm with left ventricular hypertrophy and left atrial enlargement (Fig 2). The chest roentgenogram

From the Baylor University College of Medicine, Texas Children Hospital, Houston, Texas 77025.
Received for publication Nov 27 1967
*Fellow in Pediatric Cardiology
**Assistant Professor of Pediatrics.
***Associate Professor of Pediatrics.



Fig. 1 Patient as she appeared 6 months before the emergency replacement of her mitral valve.

revealed marked cardiomegaly and left atrial enlargement along with kyphoscoliosis and pectus excavatum (Figs. 3 and 4).

The patient was admitted to Texas Children Hospital on Oct. 23 1966, for cardiac catheterization. The right heart study was normal. Left heart catheterization data included left ventricular pressure of 98/0 mm Hg with an end-diastolic pressure of 8 mm Hg. There was no pressure gradient across the aortic valve. Selective left ventricular angiocardiography showed left ventricular enlargement with severe mitral regurgitation. The aortic valve appeared normal and the thoracic aorta was normal in size.

The results of the cardiac catheterization were thought to represent mitral insufficiency with no aortic involvement. It was elected not to perform surgery and to follow her under medical management. She was scheduled for outpatient visits at regular intervals and her condition remained satisfactory. Her heart size did not increase and there was no further decompensation.

On May 2 1967 she was readmitted to Texas Children Hospital with the history of severe dyspnea, dry cough and restlessness beginning 12 hours earlier. There was no history of chest pain or abdominal pain. Examination revealed the heart rate to be 164 per minute and regular. The respirations were labored with a rate of 50 per minute. The arm blood pressure was 72/54 mm Hg. She appeared to be distressed and apprehensive. There was peripheral cyanosis. The lungs were clear. The apical impulse was found to be in the posterior axillary line. The previously described cardiac findings were again present.

Chest roentgenograms showed considerable increase in heart size compared to films taken 2 months before. The ECG revealed sinus tachycardia, left ventricular hypertrophy and left atrial enlargement. She was taken to surgery where it was discovered that the posterior leaflet of the mitral valve was flail due to the rupture of chordae tendineae. A prosthetic valve was inserted. The patient appeared to improve in the immediate postoperative period with occasional premature ventricular beats being the only observed arrythmia. However cardiac arrest occurred 17 hours after surgery and she could not be resuscitated.

Autopsy findings revealed the prosthetic valve to be in place. There were deposits of mucopolysaccharides in the cardiac valves and papillary muscle as well as acute inflammatory changes on sections through the papillary muscle. No evidence of bacterial endocarditis was found. Medial degeneration of the aorta at the root was also detected. Sections through the right and left ventricles disclosed no abnormalities.

Discussion

The cardiovascular manifestations of Marfan's syndrome have been thoroughly scrutinized by McKusick.[1,2] The initial consideration by earlier observers of this disease of structural congenital cardiac malformations such as atrial septal defect and ventricular septal defect, has shifted to a recognition of the abiotrophic nature of this condition with widespread involvement of connective tissue. Lesions of the great vessels have received particular attention. Medial degeneration of the aorta, aortic dilation, aortic insufficiency ruptured aortic sinus of Valsalva, and dissecting aneurysms and rupture of the aorta have received appropriate emphasis. Similar medial degeneration of the pulmonary artery has also been appreciated.

More recently involvement of the mitral valve in this disease has been recognized.[4] Redundancy of the mitral cusps and chordae tendineae have been observed as causes of major mitral regurgitation. Acute surgical emergencies involving the mitral

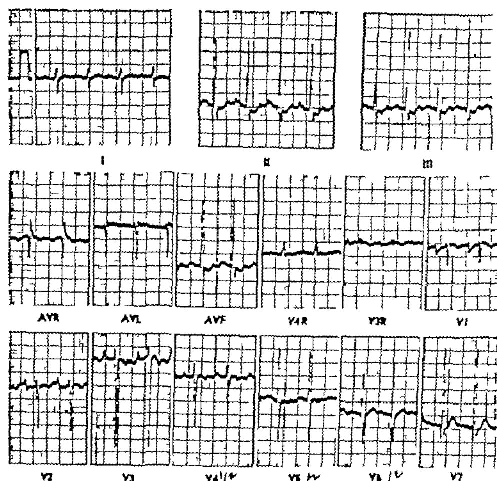


Fig. 2. ECG of patient at initial visit. This was interpreted as being consistent with left ventricular hypertrophy and left atrial enlargement.

valve have not been emphasized but the mitral valve represents a predictable source of such emergencies. Redundant chordae tendineae would appear to be predisposed to rupture as suggested by this patient and as mentioned briefly by Keith and associates. McKusick[3] has reported the autopsy finding of a partial avulsion of the posterior cusp of the mitral valve in a patient who died after an attempt at surgical repair of the ascending aorta. The present report would appear to be the first observation of rupture of mitral chordae tendineae in a child leading to acute exacerbation of congestive heart failure and emergency prosthetic valve replacement. Reports of subacute bacterial endocarditis involving the mitral valve in Marfan's syndrome should alert the physician to the further possibility of acute disruption or destruction of the valve on this basis.[7]

If diagnosis of ruptured chordae tendineae of the mitral valve is made promptly enough to undertake surgical correction and if surgical correction is immediately successful the ultimate prognosis must of course remain guarded because of the underlying diffuse connective tissue abnormality.

Summary

This report calls attention to the occurrence of acute cardiovascular surgical emergencies involving the mitral valve in Marfan's syndrome by presenting the case history of a 4-year-old girl. This patient

Fig. 3



Fig. 4



Fig. 3 Chest roentgenogram of patient at visit preceding acute episode involving mitral valve. Cardiomegaly and striking kyphoscoliosis are readily apparent.
Fig. 4 Chest roentgenogram obtained 10 hours after acute onset of symptoms. Note change in configuration of the heart.

with classical features of Marfan's syndrome and known mitral insufficiency documented by cardiac catheterization and angiocardiography had an acute episode of profound congestive heart failure which appeared to be secondary to a sudden increase in the volume of mitral regurgitation. At surgical exploration, a flail posterior leaflet of the mitral valve with ruptured chordae tendineae was discovered. The patient died 17 hours after mitral valve prosthetic replacement.

REFERENCES

1. Cooley, D. A., Bloodwell, R. D., and Hallman, G. L.: Aneurysm of the ascending aorta with aortic valvular insufficiency, Arch. Surg. 93: 396, 1966.
2. McKusick, V. A.: The cardiovascular aspects of Marfan's syndrome, Circulation 11:321, 1955.
3. McKusick, V. A.: Heritable disorders of connective tissue, ed. 2, St. Louis, 1966, The C. V. Mosby Company, chap. 3, p. 58.
4. Miller, R., Jr., and Pearson, R. J. J.: Mitral insufficiency simulating aortic stenosis. Report of an unusual manifestation of Marfan's syndrome, New England J. Med. 260:1210, 1959.
5. Segal, B. L., Tabesh, E., Imbriglia, J. E., and Likoff, W.: The Marfan syndrome. Necropsy findings in three patients with review of the cardiovascular complications, Angiology 13: 444, 1962.
6. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, ed. 2, New York, 1967, The Macmillan Company, p. 1163.
7. Bowers, D., and Lim, D. W.: Subacute bacterial endocarditis and Marfan's syndrome, Canad. M. A. J. 86:455, 1962.

Review

Metabolism of the heart in health and disease Part II*

Lionel H Opie M.D
London England

IV Metabolism of chylomicron and lipoprotein triglyceride by the heart

Serum lipoproteins The myocardial uptake of phospholipids and cholesterol appears to be insignificant[171,illegible] except for the uptake of lysolecithin[illegible] Thus, the myocardial metabolism of lipoprotein lipid resolves itself chiefly into a study of the TGFA of the chylomicra and of the very *low* density lipoproteins Like dietary TGFA in chylomicra,[illegible] endogenous TGFA carried in th very low density lipoproteins is removed from the plasma at a rapid rate by the extrahepatic tissues[illegible] while TGFA in lipoproteins of *higher density appears to be taken up* more slowly[illegible]

Utilization of exogenous triglyceride by the heart It is intrinsically difficult to measure the magnitude of TGFA uptake by the heart in situ The average myocardial O_2 uptake[illegible] of 10.4 mL per 100 grams per minute could *fully* be accounted for by the oxidation of only 5 mg of triglyceride which corresponds to about 1 per cent of the circulating total *fasting* TGFA concentration or about 7 per cent of all TGFA passing through 100 grams of the heart per minute at a coronary blood flow rate of about 100 ml per 100 grams per minute. *In the light of these calculations, it is not surprising* that no clear conclusion can be reached about the question of TGFA uptake by the heart in situ where arteriovenous differences must be measured[194]

In only one study that of Ballard and associates[illegible] *has a claim been made for a* significant uptake of TGFA by the human heart. Total (esterified and nonesterified) fatty acid uptake was determined by a method involving hydrolysis and titration From 1 5 to 11 per cent of the arterial total fatty acid was extracted by the heart

From the M.R.C. Metabolic Reactions Research Unit, Department of Biochemistry Imperial College, London S W 7 England.

Chemical abbreviations used

ATP	= adenosine-5'-triphosphate	NADP and NADPH₂	= oxidized and reduced forms of nicotinamide-adenine dinucleotide phosphate (formerly TPN and TPNH₂)
ADP	= adenosine-5'-diphosphate		
AMP	= adenosine-5'-monophosphate		
Pi	= inorganic phosphate	FFA	= free fatty acids or unesterified fatty acids or nonesterified fatty acids (NEFA)
Cyclic AMP	= cyclic adenosine-3',5'-monophosphate		
CrP	= creatine phosphate or phosphocreatine	TGFA	= triglyceride fatty acids
NAD and NADH₂	= oxidized and reduced forms of nicotinamide-adenine dinucleotide (formerly DPN and DPNH₂)	G-6-P	= glucose-6-phosphate
		DNA and RNA	= deoxyribonucleic acid and ribonucleic acid

*Part I appeared in the November 1968 issue and Part III will appear in future issues of this JOURNAL. A complete list of references will appear after Part III.

January 1969 Vol 77 No. 1 pp 100-1--

and which accounted for 50 to 482 per cent of the concurrently measured oxygen usage. These values on only 7 patients have a very wide scatter. The results were also compared with the simultaneously determined FFA extraction, to yield the uptake of esterified fatty acid and on this indirect basis it was suggested that esterified fatty acids accounted for over half of the total fats extracted by the myocardium. In 2 other studies,[171,234] the plasma triglyceride fraction was separated and measured directly; the failure to show myocardial uptake from arterial levels of 60 to 90 mg. per 100 ml. of plasma appears to be a trustworthy result but a metabolically significant uptake could still escape accurate measurement.

In the dog heart in situ Ballard and associates,[179] found that the uptake of total esterified fatty acid (measured indirectly as in their studies on man) could account for nearly 100 per cent of the concurrent oxygen uptake. Although this figure is derived from 34 dogs and less open to criticism than the results found in humans (see above), either substantial technical error or myocardial lipid storage to the order of 25 grams per day is suggested.[181] In other studies on dogs, direct and separate measurements of esterified fatty acids have been made. Uptake of esterified fatty acids can account for 56 per cent of the oxygen uptake in one study[234A] but this result contradicts a previous study by the same author[236] in which no uptake of esterified fatty acid was found, albeit by a less sensitive method. Furthermore, in other studies, no detectable uptake of TGFA by the dog heart in situ is reported.[21,30,32]

In the isolated perfused heart, the situation is different. TGFA uptake and oxidation have been shown repeatedly.[214,231,233,234,235] Gousios and co-workers,[234] and Delcher and colleagues,[235] report high rates of uptake of TGFA in lipoproteins of d < 1.006 comparable to rates for FFA uptake. However, in other studies,[14,31,234] the rates of TGFA uptake and oxidation were lower. As in many other studies, when the isolated heart is perfused with a single substrate, a sufficiently high concentration of that substrate may result in rates of oxidation which account for the major part of the myocardial oxygen uptake. Such results do not, therefore, prove that TGFA is a major myocardial fuel in vivo.

The effect of the nutritional state of the animal on the rate of myocardial triglyceride uptake is still unresolved. After an injection of [14]C-labelled TGFA as chylomicra into rats, the percentage of label that is recovered in the heart is increased about 3 times in starved as compared to carbohydrate-fed rats.[237] Gousios and co-workers[234] suggest that fasting accelerates myocardial uptake and oxidation of d < 1.006 lipoprotein TGFA in the perfused rabbit heart, but if allowance is made for the higher TGFA concentration in perfusate prepared from rabbits in the fed state, then the absolute TGFA uptake and oxidation may be greater in the fed state. In isolated rat hearts there are minimal differences between chylomicron TGFA uptake and oxidation in fed and fasted states.[198,233] Thus, the influence of diet on TGFA usage by the animal heart is still unresolved.

Little is known about the interaction between triglyceride and other myocardial fuels such as FFA, lactate, and glucose. TGFA, as chylomicra, can decrease the rate of glucose uptake by the isolated perfused heart, suggesting that fatty acids derived from this source have an effect similar to exogenous FFA in controlling myocardial glucose metabolism.[233] Thus it is likely that TGFA, if taken up, can compete with other myocardial fuels for uptake by the isolated perfused rat heart.

When glucose and labelled chylomicra are simultaneously infused into fasting rats, the rate of chylomicron TGFA oxidation is reduced by only 16 per cent below the control, the myocardial respiratory quotient rises relatively little, but cardiac glycogen nearly doubles.[239] These results suggest glucose storage rather than oxidation, and possibly preferential oxidation of chylomicron TGFA. However, these rats were fasted for 24 hours before use and the respiratory quotient never rose above 0.82. By contrast, the myocardial respiratory quotient approaches unity in the fed state[4,42] which argues against substantial lipid and triglyceride oxidation by the heart in the fed state in vivo.

At present, it appears that competition between TGFA and glucose is probably similar to that between FFA and glucose, provided that the fatty acids derived from TGFA or from albumin bound FFA enter the myocardial cells at similar rates.

Role of clearing factor lipase Triglyceride is hydrolyzed during its passage from the blood stream to the heart cells. Extra hepatic tissues do not take up appreciable amounts of intact chylomicron glyceride as judged from the fate of doubly labelled chylomicron TGFA.[340] Furthermore, the hearts of rats injected with triglyceride labelled in glycerol (^{14}C) and palmitate (^3H) moieties, initially retain relatively more ^3H than ^{14}C.[341] In the isolated rat heart perfused with doubly labelled tri palmitin palmitate radioactivity is also more readily retained by the heart.[31] Evidence for lipolysis of triglyceride is also provided by an increase in FFA in the heart[31,334] or in the medium[314,315] during perfusion of the isolated rat heart with chylomicra. Morphological evidence favors a change in chylomicron structure. In rats previously injected with chylomicra, the capillary lumen of several tissues (including the heart) contains chylomicra often in close association with the endothelial sur face there is, however no evidence for the intact passage of chylomicra across the vascular endothelium.[341A] Thus it is inferred that the structure of chylomicra must change before leaving the intravascu lar space. It is attractive to implicate the clearing factor lipase thought to be situated on the cell surface or on the capillary wall in these processes.[342,343]

Clearing factor lipase (= lipoprotein lipase) probably plays an important role in the physiological removal of triglyceride from the blood by the extrahepatic tissues.[342] First demonstrated in an acetone powder of rat myocardium by Korn[344] it also occurs in *human heart tissue*.[345] Clearing factor lipase plays a role in TGFA metabolism by the heart as shown by decreased recovery of label from ^{14}C TGFA in $^{14}CO_2$ and in myocardial FFA after discharge of a substantial portion of myocardial clearing lipase by a prior heparin perfusion.[136] At present the release of clearing factor lipase by heparin has no *obvious physiological significance for the* activity of this enzyme in vivo.

Hormones may influence myocardial clearing factor lipase activity which is increased in homogenates taken from rats treated with thyroid hormone or epinephrine[346] and decreased in homogenates from hypothyroid rats.[347] In alloxan-diabetes, the heparin-released lipolytic activity of rat heart more than doubles, and activity is reduced to normal by insulin treat ment.[348] The existence of conflicting data[348,319,364] makes it difficult to postulate a major role for dietary factors in the control of myocardial clearing factor lipase.

It has also been suggested that increased myocardial clearing factor lipase activity may be an adaptation to an increased work load as after thyroid or epinephrine stimulation[346] or during development.[52] Similarly the clearing factor lipase of rat myocardium increases nearly twofold after prolonged exercise.[353] However increased cardiac work induced by experimental hypertension in aortic constriction is not associated with alterations in myocardial clearing factor lipase activity.[347] Further *more, the utilization of TGFA by the* isolated rat heart is not increased by muscular work. When the oxygen uptake of the perfused rat heart is doubled by allowing the left ventricle to perform mechanical work, the rate of oxidation of ^{14}C labelled chyle does not increase.[144] This suggests that as during increased contractility following epinephrine stimulation[352] alternate substrates are oxidized by the isolated rat heart in preference to chyle lipids during increased work.

What are needed are further definitive attempts to correlate clearing factor lipase activity with TGFA uptake by the heart in experimental conditions allowing such a comparison Special attention would also have to be paid to the techniques for assay *of the enzyme* to ensure that the lipase being studied is in fact clearing factor lipase and not one of a number of other lipase activities.[153] It must be emphasized that the activity of clearing fac tor lipase is not easy to measure and full appreciation of the published literature requires a careful examination of the con ditions used in the assay

In summary clearing factor lipase is thought to be implicated in the uptake of TGFA by the myocardium. This enzyme may be sensitive to hormonal influences. Detailed assessment of the factors controlling clearing factor lipase activity is, however not possible at present.

TGFA metabolism in pathological states A prolonged intravenous infusion of ethanol or intracoronary infusion of epinephrine into dogs leads to a substantial increase in the TGFA uptake by the heart [illegible]. The left ventricular triglyceride content rises, suggesting that the rates of TGFA uptake exceed the myocardial oxidative capacity for intracellular fatty acid. The mechanism of the increased TGFA uptake following ethanol and epinephrine stimulation is unknown but increased clearing factor lipase activity[illegible] or increased permeability of the capillary or cell membrane to TGFA are possibilities. Thus, TGFA uptake by the heart can be substantial in these pathological states.

In alloxan-diabetes in rats clearing factor lipase activity of the heart increases,[illegible] while TGFA uptake and oxidation by the isolated heart do not.[illegible] The increased myocardial triglyceride content in this condition can rather be ascribed to increased uptake of circulating FFA by the heart in situ.[illegible]

Conclusions Adequate evidence for TGFA uptake by the human heart has not been produced and the rates of TGFA uptake and oxidation found in isolated perfused hearts do not allow extrapolation to prove a significant TGFA uptake in vivo. The enzyme clearing factor lipase (= lipoprotein lipase) is implicated in TGFA uptake by the isolated heart. There is some evidence that hormonal factors may be concerned in both TGFA utilization and clearing factor lipase activity

Table I *Competition between glucose and palmitate in isolated perfused rat heart*

(*A*) *Substrate studied* Concn. mM	(*A*) Concn. gram/100 ml.	(*B*) *Additional substrate* Concn. mM	(*B*) Concn. gram/100 ml	*Nutritional state*	*O.E.R. of (A) (%)*	*Change in oxidation of (A) (%)*	*Author*
glucose 11		none		fed	26	control	Willebrands[illegible]
glucose 11		mixed FFA 1.0	albumin 1.5	fed	20	−23	Willebrands[illegible]
glucose 10		none		fed	43	control	Shipp et al.[illegible]
glucose 10		palmitate 0.7	albumin 0.5	fed	14	−68	Shipp et al.[illegible]
glucose 10		palmitate 0.5	albumin 0.5	starved	—	−71	Shipp[illegible]
glucose 5		palmitate 0.5	albumin 0 5	starved	—	−82	Shipp[illegible]
glucose 5		palmitate 0 5	albumin 3.0	starved	—	−72	Shipp[illegible]
glucose 5		palmitate 0.7	albumin 0.5	starved 96 hrs.	—	−75	Opie et al.[illegible]
glucose 7.5 insulin 2 mμ/ml.		palmitate 0 3	albumin 0.5	fed	—	−56	Opie, unpublished data
mixed FFA 1.0	albumin 1.5	none		fed	32	control	Willebrands[illegible]
mixed FFA 1.0	albumin 1.5	glucose 11		fed	37	−29	Willebrands[illegible]
palmitate 0 75	albumin 0.5	none		fed	57	control	Opie et al.[illegible] and Evans et al.[illegible]
palmitate 0.75	albumin 0.5	glucose 5		fed	49	−14	Opie et al.[illegible]
palmitate 0.75	albumin 0.5	glucose 5		starved 96 hrs.	57	0	Opie et al.[illegible]
palmitate 0.5	albumin 0 5	glucose 5		starved	—	+47	Shipp[illegible]

In Tables I to III, O.E.R. = oxygen extraction ratio, here defined as the percentage of the total oxygen uptake accounted for by oxidation of the substrate in question; change in oxidation of A is percentage change, taking value without addition of substrate B as 100 per cent. For criticism of O.E.R., see text. In all tables, dash (—) indicates absence of data.
*Not significant difference.

but a more detailed assessment of the situation must await the appropriate experiments.

V Substrates for oxidative metabolism

Arguments from substrate couples in the isolated perfused rat heart The competition between various substrates for the oxygen uptake of the isolated perfused heart has been studied very extensively (Tables I to III) using one or more of the following methods (1) assessment of the contribution of a substrate to the oxidative metabolism of the heart (2) the effect of alternative substrates on this contribution and (3) the inducement of metabolic blocks in the pathways of substrate degradation by an additional substrate

Many of these studies can be criticized for one or more of the following reasons. First it is usually assumed that the myocardial uptake (qO_2) is independent of the exogenous substrate because initial reports suggested that the qO_2 of the isolated perfused rat heart is not affected by the addition of glucose (with or without insulin) succinate or β-hydroxybutyrate.[34] However FFA short chain fatty acids, TGFA lactate, pyruvate, and acetoacetate can all in certain circumstances cause substantial increases in the qO_2.[illegible] In contrast, in other studies, the addition of lactate or acetoacetate has decreased the qO_2 slightly[33, 44] Taken together these findings stress that the nature of the substrate *can* alter the qO_2 Further factors influencing the qO_2 of the isolated rat heart are the coronary flow rate and perfusion pressure the heart rate and the extracellular Ca^{++} concentration [illegible] The qO_2 must, therefore be measured under the exact mechanical and metabolic conditions of the experiment.

Table II Competition between pyruvate and other substrates in isolated perfused rat heart

(A) Substrate studied		(B) Additional substrate		Nutritional state	O.E.R. of (A) (%)	Change in oxidation of (A) (%)	Author
Concn. mM	Concn. gram/100 ml	Concn. mM	Concn. gram/100 ml				
pyruvate 11		none		fed	53	control	Willebrands[illegible]
pyruvate 11		mixed FFA 1	albumin 1.5	fed	63	+19	Willebrands[illegible]
pyruvate 5		none		fed	42	control	Willebrands[illegible]
pyruvate 5		mixed FFA 1	albumin 1.5	fed	12	−77	Willebrands[illegible]
pyruvate 5		palmitate 0 8	albumin 0.5	fed	—	−24	Evans et al.[79]
pyruvate 5		palmitate 0 8	albumin 0.5	starved	—	−56	Evans et al.[79]
pyruvat 5		palmitate 1 1	albumin 3.0	starved	—	−38	Evans t al.[79]
pyruvat 4		palmitate 0 75	albumin 2.0	fed	—	−71	Garland et al.[illegible]
pyruvate 1		palmitate 0.75	albumin 2.0	fed	—	−78	Garland et al.[illegible]
pyruvate 1		butyrate 4		fed	—	−78	Garland et al.[illegible]
pyruvate 10		glucose 11		fed	—	nchanged	Willebrands[illegible]
pyruvate 10		acetate 10		fed	60	−33	Williamson[illegible]
pyruvate 11		acetoacetate 5		fed	20	−61	Willebrands[illegible]
pyruvat 4		DL-hydroxybutyrate 5.5 mM		fed	—	−66	Garland et al[illegible]
mixed FFA 1	albumin 1.5	pyruvate 5		fed	—	−37	Willebrands[illegible]
palmitate 0 75	albumin 0.5	pyruvate 5		starved	—	−39	Evans et al.[79]
palmitate 0.5		pyruvate 5		starved	—	− 6	Shipp[illegible]
palmitate 0.27		pyruvate 10		fed	—	−76	Olson[illegible]
glucose 11		pyruvate 10		fed	—	−62*	Willebrands[illegible]
glucose 5		pyruvate 5		starved	—	−62	Opie npublished data
acetate 10		none		fed	74	control	Williamson[illegible]
acetate 10		pyruvate 10		fed	35	−53	Williamson[illegible]

*Estimated.

Another assumption sometimes made is that all glucose or pyruvate not forming lactate is oxidized provided that allowances are made for any changes in the glycogen content.[illegible] While studies with ^{14}C-labelled pyruvate show that $^{14}CO_2$ and lactate formation account for 87 to 100 per cent of the pyruvate uptake when palmitate is added as additional substrate or in the starved state the recovery of label is as low as 60 per cent.[78] The assumption that all glucose not forming lactate or glycogen is oxidized can lead to inaccuracies caused by (1) the failure to measure glycolytic intermediaries which can account for up to one-quarter of the uptake of ^{14}C-glucose, depending on the experimental conditions, and (2) the lag in glucose oxidation during the first 15 minutes of perfusion.[illegible] From the latter point of view the experiments of Williamson[illegible] are less open to criticism because he used a 15 minute preperfusion period.

The most serious defect of many competition studies is the failure to simulate physiological conditions. An example is the interaction of glucose and FFA metabolism in the isolated rat heart. In 1961 Shipp and co-workers[illegible] produced direct evidence that palmitate (0.4 mM complexed to albumin 0.5 gram per 100 mL) reduced the oxidation of ^{14}C-glucose to one-tenth of the control value while glucose left the oxidation of ^{14}C palmitate unaltered. Further work on the same preparation has shown that *under specified conditions* the addition of palmitate to the perfusate (1) increases lactate formation from glucose, (2) stimulates the incorporation of glucose carbon into glycogen, and (3) inhibits the insulin induced increase of glucose uptake and decreased the rate of glucose uptake.[illegible] Pyruvate radio-isomers have been used to show that a defect of pyruvate decarboxylation is induced by the presence of FFA.[7] It has therefore been suggested that the concurrent oxidation of FFA by heart muscle can actually control the intracellular fate of glucose especially at the level of pyruvate entry into the tricarboxylic acid cycle.[illegible]

Table III *Other competition studies*

(*A*) *Substrate studied* Conc. mM	(*B*) *Additional substrate* Concn. mM	*Nutritional state*	*Change in oxidation of* (*A*) (%)	*Author*
L-lactate 5	glucose 5	fed	−25	Williamson
DL-lactate 12	acetate 5	fed	−88	Davis and Quastel
glucose 5	lactate 5	fed	total inhibition	Williamson
glucose 5	acetate 5	fed	−92	Davis and Quastel
glucose 5	acetate 5	starved	−91	Shipp
palmitate 0.5 albumin 0.5 gram/100 mL	acetate 5	starved	−34	Shipp
acetate 5	glucose 10	fed	no change	Davis and Quastel
acetate 5	propionate 5	fed	no change	Davis and Quastel
mixed FFA 1.0 albumin 1.5 gram/100 mL	acetoacetate 10	fed	−61	Willebrands
palmitate 0.27 albumin 2.0 gram/100 mL	acetoacetate 10	fed	−77	Olson
acetoacetate 10	mixed FFA 1	fed	−42	Willebrands
acetoacetate 5	glucose 5	fed	no change	Williamson
acetoacetate 5 insulin 2 mu./mL	glucose 5	fed	−33	Williamson
glucose 5	propionate 5	fed	−38	Davis and Quastel
glucose 5	butyrate 2.5	fed	−94	Davis and Quastel
glucose 5	pentanoate 5	fed	−92	Davis and Quastel
glucose 5	heptanoate 1	fed	−79	Davis and Quastel

Davis and Quastel used isolated guinea pig heart; all other data obtained on rat heart.

However the majority of these studies were conducted on hearts from fasted rats, with FFA complexed to 0.5 gram per 100 ml. of albumin and therefore a higher than normal FFA:albumin ratio which encourages FFA usage.[173] More physiological albumin concentrations, the fed state, higher glucose and lower FFA concentrations result in a lesser suppression of glucose oxidation (Table I).[244]

Randle and his co-workers[14,22,60,300,240] have studied the effects of fatty acids and ketones on the concentration of glycolytic intermediates of rat heart muscle and on the effective activities of key enzymes. Their work delineates an induced defect in glycolysis at the level of phosphofructokinase which is thought to be inhibited by the increased circulating citrate levels found in the heart during enhanced respiration of fatty acids and ketones. The decreased glucose uptake has been related to a secondary decrease in the effective activity of hexokinase. Glucose uptake and phosphorylation are significantly reduced by a FFA concentration of 0.5 mM which is within the normal range while the albumin (4 grams per 100 ml.) concentration the glucose concentration and the nutritional and hormonal conditions are such that these experiments appear to have physiological significance.

Evidence for substrate competition in the dog heart in situ is that glucose uptake is decreased when the FFA uptake increased during a simultaneous infusion of glucose and noradrenaline.[296] Other studies show that an infusion of lactate depresses glucose utilization by the dog heart in vivo while lactate and FFA can inhibit the utilization of each other.[244]

On the basis of the competition studies in the rat heart, the fundamental concept of a glucose-fatty acid cycle has been introduced by Randle and co-workers.[298] Stated briefly the hypothesis is that enhanced respiration of FFA and ketone bodies (as in carbohydrate deprivation) suppresses the effect of insulin on glucose transport in the heart and other muscles conversely increased circulating glucose and insulin concentrations (as found after carbohydrate feeding) reduce the rate of release into the circulation of FFA from adipose tissue. While this hypothesis provides physiological meaning for substrate competition in the heart, it does not allow for any direct effect glucose might have on myocardial FFA metabolism in a combination of conditions favoring maximal glucose utilizations such as a high glucose concentration the addition of insulin, the fed state and FFA concentrations below 0.4 mM bound to albumin 4 grams per 100 ml. (the physiological albumin concentration in the rat). In similar conditions palmitate 0.3 mM suppresses glucose uptake of the isolated rat heart by only 20 per cent[14] and the FFA uptake by the heart in situ is negligible.[177] It has in fact been suggested[244] that glucose (8.5 mM.) can halve the rate of oxidation of palmitate (1 mM bound to albumin 5 grams per 100 ml.) by the isolated hearts of fed rats, whereas palmitate does not affect glucose oxidation. Even allowing for the expectation that this concentration of glucose would depress palmitate oxidation to some extent, the failure of such a high palmitate concentration to influence glucose metabolism in this study is unexpected.

From studies with various substrate couples (Tables I to III) it has generally been concluded that acetate, ketones, short-chain fatty acids, lactate, and pyruvate are oxidized in preference to glucose.[19,44,129,229,241,257] However as already stressed by Olson[243] many possible conclusions can be made concerning the preferential usage of a fatty acid when compared with a carbohydrate or carbohydrate-derived acid according to the concentrations and experimental conditions used. Competition between unphysiologically high concentrations of various substrates may have considerable academic interest, but such studies are not invariably directly relevant to the problem of substrate-choice of the heart in vivo. More meaningful data might be obtained from the perfused heart by using substrate and hormonal conditions more closely corresponding to those found in vivo.

It has been concluded that lipid (whether endogenous or exogenous) is a major energy source of the heart.[170,176,141,238,240,244] It must however be recalled that the competition between the 2 major substrates of the heart in vivo lactate and FFA (Table IV) has not been fully studied while

Table IV. Effect of nutritional state on fuel for oxidative metabolism of the human heart. Percentage of oxygen uptake accounted for if various substrates are fully oxidized

Conditions	*Author(s)*	*Glucose*	*Pyruvate*	*Lactate*	*Total CHO*	*FFA*	*Ketones*	*Amino acids*	*Respiratory quotient*
Glucose and insulin	Gordon and Cherkes[illegible]	—		—	—	none		–	—
"Feeding"	Olson and Piatnek[illegible]	—		—	92	5		–	approaches 1 0
Postprandial	Goodale et al.[illegible]*	68	4	28	100	—		–	0 94
Fasting few hours	Keul et al.[illegible]†	31	2	28	61	34	5	0	—
Same, during exercise	–do–	16	0	61	77	21	2	0	—
Same, with recovery	–do–	21	2	36	59	36	3	0	—
Fasting overnight	Bing[illegible]‡	18	1	16	35	(67)‖	5	6	—
	Gordon and Cherkes[illegible]§	—		—	—	50	–		—
	Goodale et al.[illegible]	23	3	8	34	—	–		0 74
	Olson and Piatnek[illegible]‡	—		—	30	58	–	–	—
	Harris et al.[illegible]	56	1	10	67	66	–	–	—
	Rudolph et al.[illegible]	15	1	13	29	70	9	–	—
	Willebrands[illegible]	30	0	8	38	58	–		—
	Mean values	28	1	11	39	60	7		

Abbreviations: CHO, Carbohydrate; FFA, free fatty acids.
*Subjects studied 2 to 3 hours after a light, low-fat breakfast.
†Subjects studied in the early afternoon after a light breakfast.
‡Exact conditions not specified; overnight fast assumed.
§Includes data of Gordon.[illegible]
‖Total fatty acid.

glucose-palmitate studies are still incomplete and to some extent contradictory.

Arguments from studies on red and white skeletal muscle. Patterns of metabolism in red and white skeletal muscle are relevant to the question of substrate preferences in the heart, because heart muscle can be regarded as an extreme type of red muscle from the metabolic point of view.[illegible] Red fibers have high lipid and lipase contents, in contrast to high contents of glycogen and glycolytic enzymes in the white muscle. Red fibers take up and utilize lipid rather than carbohydrate for their energy metabolism.[illegible] It follows that the heart is metabolically more reliant on the oxidative metabolism of lipids than on glycolysis for its energy requirements.

The hypothesis linking red muscle with lipid-dependency is also applicable to the difference between adult and fetal heart tissues. In general, primitive muscle is white and glycogen-dependent.[illegible] Fetal heart tissue is low in cytochrome oxidase, rich in glycogen, and resistant to anoxia.[illegible] Furthermore, the newborn rat heart has a greater capacity to oxidize glucose than adult tissue, whereas its capacity to oxidize long chain fatty acid is low because of poor activity of acyl CoA-carnitine transferase and a low content of carnitine.[illegible] Thus fetal heart tissue has the metabolic properties of white muscle, is more dependent on glycolysis and hence is more resistant to anoxia.

Effect of heart work on substrate competition. Until recently, it has usually been assumed that the Langendorff preparation is nonworking, with an empty left ventricle. However, there are wide pressure fluctuations when the left ventricle pressure is measured by an intraventricular balloon.[illegible] The intraventricular balloon measures isovolumic work, which increases with the coronary flow and the perfusion pressure; when the latter exceeds 160 to 200 mm. Hg, the left ventricle fails.[illegible] Opie[illegible] could not separate the effects of

increased coronary flow rate and of increased perfusion pressure, but recently Lochner and associates[77] found that the perfusion pressure is the major determinant of isovolumic work. It was noted by both workers that the peak systolic pressure recorded on the isovolumic balloon was considerably below the perfusion (aortic) pressure at high perfusion pressures. Morgan and co-workers[illegible] have established that in the Langendorff preparation without a left ventricular balloon, the peak pressure recorded from a small needle penetrating the left ventricle equals the perfusion pressure. This pressure development may be secondary to the accumulation of perfusate in the left ventricle from Thebesian drainage or from minor degrees of aortic incompetence such perfusate would accumulate and distend the left ventricle which then empties itself through the aortic valve against the perfusion pressure In the experiments of Opie[77] and Lochner[77] when the balloon was inserted into the ventricle via the left atrium severe mitral incompetence would allow any perfusate reaching the left ventricle to *drain readily thus, decreasing the extent* of systolic pressure development. The above observations show that (1) the Langendorff preparation is doing external mechanical work although it is difficult to measure this in classical terms of external work, and (2) an increased perfusion pressure increases development of peak pressure in the left ventricle albeit to a lesser extent when the mitral valve is incompetent. Therefore studies at various perfusion pressures can be used to show the effect of increased left ventricular work on substrate utilization Over a wide range of isovolumic work, oxidation of ^{14}C palmitate (0 7 mM albumin 1 gram per 100 ml) accounts for about 60 per cent of the total qO_2 while the oxidation of ^{14}C-glucose accounts for 25 per cent of the qO_2[77] *When left ventricular work is* increased by filling of the left atrium from an atrial cannula glucose utilization still only accounts for 36 per cent of the qO_2[illegible] Furthermore the addition of palmitate to the perfusate eliminates the increase in *glucose uptake* induced by high atrial pressures or by an increased perfusion pressure *in the Langendorff preparation*[illegible]

Similarly palmitate (0.5 mM albumin 3 grams per 100 ml) substantially inhibits glucose uptake *in both working and Langendorff* isolated rat heart preparations.[illegible] There is thus far no evidence that increased left ventricular work, however produced is a major factor in the control of competition between glucose and palmitate for oxidative metabolism in the heart.

Energy balance of the human heart. This has been assessed by coronary sinus catheterization and by comparison of the arteriovenous differences across the heart of various substrates with the simultaneous uptake of oxygen The oxygen extraction ratio (O E.R.) of a substrate is found by dividing the amount of oxygen theoretically required for complete oxidation of that substrate by the oxygen uptake measured on the same samples. This assumption suffers from the defect that substrates almost certainly have nonoxidative fates which may be especially important when substrates are competing for oxygen This criticism does not apply when the O E.R. is obtained by actually measuring the rate *of oxidation of the substrate in question,* as in some experiments cited in Table I At present, however the oxidation extraction ratio is the only available way of assessing the energy balance of the normal human heart. Two carbohydrate substrates glucose and lactate and one noncarbohydrate substrate, FFA, can account for virtually all of the myocardial oxygen uptake (Table IV) In fasting conditions, the mean oxidation extraction ratios are FFA, 60 per cent glucose, 28 per cent and lactate 11 per cent and the respiratory approaches 0 70 It is not clear why Harris and co-workers[illegible] obtained a much higher value for glucose extraction. After a shorter fast of only a few hours, the FFA contribution falls to 34 per cent and that of carbohydrate rises to about 60 per cent. Immediately after a meal or during the administration of glucose and insulin the contribution of FFA becomes negligible glucose is the main fuel and the respiratory quotient approaches unity

The increased energy demands of short periods of exercise are met by an increased coronary blood flow[171] and increased extraction of carbohydrate substrates especially

of lactate.[illegible] The conclusion of Harris and co-workers[illegible] that the glucose becomes the major source of energy in exercise must be assessed together with their very high values for glucose extraction in the resting state (Table IV)

Thus carbohydrate is a major fuel at least during significant parts of the 24-hour day and especially during bursts of exercise. The frequently quoted statement that fatty acids are the major fuel of the heart in vivo[1] applies chiefly to overnight fasting conditions (Table IV) To determine the major myocardial substrate, over 24 hours, of normal humans doing average amounts of exercise and eating average diets would be very difficult. Suitable data could however be obtained on unanesthetized dogs studied during chronic coronary sinus catheterization [illegible]

Conclusions From a review of data on substrate competition in the isolated perfused heart, and from the results of coronary sinus studies in man it is concluded that many observations have been made in experimental conditions favoring the utilization of lipid as a major energy source of the heart Until further experiments are carried out it remains a possibility that the role of lipid as fuel for the heart metabolism has been overemphasized

VI. Mitochondrial metabolism

Permeability barriers Cytoplasmic NADH may be generated in heart tissue (1) by glycolysis, especially during anoxia[illegible] or (2) by conversion of lactate (taken up from the circulation) to pyruvate before mitochondrial oxidation. The rate of lactate uptake by the human heart can reach 5 μM per gram of wet weight per minute (from the data of Carlsten and associates,[171] and allowing in this calculation for a maximum coronary blood flow of 250 ml. per 100 gram heart per minute during exercise) while in the isolated rat heart, perfused with lactate as the sole substrate, the uptake can reach about 1 μM per gram of wet weight per minute.[illegible] Thus, cytoplasmic NADH must subsequently be removed at similar rates to avoid a change in the cytoplasmic redox state.

The route of disposal of cytoplasmic NADH in most tissues is entry into mitochondria by way of the α-glycerol phosphate (glycerol P) shuttle whereby cytoplasmic dihydroxyacetone phosphate is converted to glycerol P which enters the mitochondria to be oxidized by glycerol P oxidase and the respiratory chain The dihydroxyacetone produced diffuses back into the cytoplasm.[illegible] In the heart however it initially appeared that the activities of the 2 enzymes necessary for the glycerol-P shuttle were only about one tenth of the corresponding activities of mixed skeletal muscle [illegible] Similarly the activity of glycerol P oxidase of mitochondria from red skeletal muscle is about one tenth that of white skeletal muscle[illegible] and it is red muscle that resembles heart metabolically [illegible] The low glycerol P oxidase activity in the heart would make it unlikely that cytoplasmic NADH could be removed sufficiently rapidly during maximal rates of lactate uptake. This conclusion may need revision in the light of a recent report that heart muscle contains up to half the activity of glycerol-P oxidase found in skeletal muscle.[illegible] It should be emphasized that the activity of this enzyme is measured indirectly

The possibility has been raised that $NADH_2$ can directly enter heart mitochondria.[illegible] For example, isolated rabbit heart mitochondria can oxidize extramitochondrial NADH albeit at rather low rates,[illegible] and pigeon heart mitochondria oxidize $NADH_2$ at concentrations similar to those thought to prevail in the cell [illegible] Two technical problems arise. First the mitochondria might be contaminated by fragments with NADH oxidizing capacity This possibility has virtually been excluded by electron microscopy in one study [illegible] Second isolated heart mitochondria are to some extent morphologically abnormal even when prepared under optimal conditions.[illegible] It is, therefore difficult to extrapolate from results obtained with isolated mitochondria to the intact cell and the question of direct NADH oxidation by mitochondria in the intact heart cell remains open.

Isolated heart mitochondria can accumulate K^+ Ca^{++} Mg^{++} Mn^{++} and Pi against a concentration gradient by an energy-linked process.[illegible] This whole

field has recently been reviewed by Lehninger and colleagues.[illegible] Accumulation of such ions may (at least in part) be driven by *oligomycin insensitive respiration which* is thought to generate a category of high energy compounds not on the main pathway of oxidative phosphorylation.[illegible] The uptakes of Ca^{++} and Mg^{++} have several features in common.[illegible]

The physiological significance of cation flux across the mitochondrial membrane is discussed in detail by Rasmussen and Ogata.[illegible] Among the possibilities are that mitochondrial cation transport might be important in the maintenance of ionic compartmentation in the cell and that ionic fluxes could control the metabolic rate by influencing the degree of coupling of oxidative phosphorylation.

Regulation of citrate cycle activity. Control at the level of citrate is suggested because the citrate content of the rat heart is increased several times during perfusion with fatty acids or ketone bodies, or when alloxan-diabetic hearts are perfused with glucose.[illegible] Contents of citrate precursors are increased; thus, increased citrate content may reflect increased formation from acetyl CoA and oxaloacetate by citrate synthase. The increased acetyl CoA is *derived from the fatty acid moiety;* the source of the oxaloacetate may be transamination from aspartate.[illegible] Citrate accumulation could also result from decreased removal by aconitase and isocitrate dehydrogenase or by the citrate cleavage enzyme. These possibilities are discussed later in this section.

Palmityl-CoA inhibits citrate synthase *from pig heart noncompetitively* with respect to acetyl CoA; the Ki (4 μM) is not far off the physiological content of acyl CoA in the heart.[illegible] However citrate synthase does not appear to be inhibited even by the levels of palmityl CoA found during fatty acid oxidation as shown by the normal or increased myocardial oxygen uptake;[illegible] hence, there must *either be deinhibiting factors* at work such as divalent metal ions[illegible] or long-chain acylcarnitine derivatives,[illegible] or oxaloacetate itself[illegible] or else the concentration of palmityl CoA actually available to the enzyme must be below the inhibitory concentration. Pig heart citrate synthase is also inhibited by triphospho- and diphosphonucleotides in the order ATP > GTP > ADP > GDP; the inhibition by ATP *(3 to 13 mM)* is competitive with respect to acetyl CoA.[illegible] Relief of the ATP inhibition by divalent metal ions may be explained by chelation.[illegible] The inhibition of citrate synthase by ATP may indicate a regulating mechanism whereby decreased ATP concentrations, such as could be expected after increased myocardial work might accelerate the citrate cycle.

The activity of the citrate cleavage enzyme (ATP citrate lyase) may have to be considered in relating citrate concentrations to those of its precursors. Although the citrate cleavage enzyme is virtually absent in the rat heart tissue, it occurs in appreciable amounts in the chicken, rabbit, and pig heart.[illegible] Thus far nothing is known about the regulation of the activity of this enzyme in the heart.

The equilibrium of the aconitase reaction, as reflected in the citrate/isocitrate ratio, is (in the rat heart tissue) sensitive to bivalent ions such as Ca and Mg; they may act by binding with citrate.[illegible]

Control at this level of isocitrate dehydrogenase (IDH) is suggested by the following evidence. IDH occurs in forms which are NAD and NADP linked *(D-IDH and* T-IDH) respectively. The kinetic properties of D-IDH are compatible with allosteric control and it is thought to act as a regulatory enzyme.[illegible] The activity of the purified enzyme from the beef heart is enhanced by ADP, which decreases the Km for isocitrate. The enzyme is inhibited by ATP and NADH, and NAD relieves, while $NADPH_2$ potentiates the $NADH_2$ inhibition.[illegible]

Thus, alterations in the mitochondrial ATP/ADP and $NAD/NADH_2$ ratios could regulate D-IDH activity. There is evidence for such control in cardiac mitochondria oxidizing citrate[illegible] and in the perfused rat heart during fatty acid respiration and during anoxia.[illegible]

Other potential controls of the citrate cycle are at α-oxoglutarate dehydrogenase, which may be inhibited by succinyl CoA and $NADH_2$,[67] and at succinate dehydrogenase and malate dehydrogenase which may be inhibited by oxaloacetate.[illegible] There is also some evidence for the control of malate

dehydrogenase by the $NADH_2$ level in the perfused heart.[illegible]

In summary, there are several possible mechanisms controlling levels of citrate cycle intermediates in the heart including (1) the rate of citrate synthesis, which is increased under conditions (such as alloxan-diabetes) giving rise to increased formation of precursors, (2) the rate of NAD-dependent IDH activity, which may be affected by the ATP/ADP and $NADH_2$/NAD ratios, and (3) the level of oxaloacetate which may inhibit dehydrogenases and increase citrate synthase activity by virtue of its being a substrate. One of the reasons for obscurity about the role of oxaloacetate is the difficulty of its measurement.[illegible] It appears that the rate of ATP usage by contraction and the rate of ADP and NADH usage by oxidative phosphorylation could be instrumental in relating contractile activity to control of the initial steps of the citrate cycle. It must be emphasized that knowledge of the control of the citrate cycle is still in its infancy and that the suggested control mechanisms are not nearly as well defined as in the case of the control of glycolysis.

Compartmentation of adenine nucleotides. Klingenberg and colleagues[illegible] have proposed that about half the mitochondrial space, probably the cristae-space, is permeable to exogenous adenine nucleotides and uptake is proportional to the external concentrations. Endogenous nucleotides, which are probably located in the matrix-space, are exchanged with exogenous nucleotides by a "swingdoor" mechanism which may be located at the matrix/cristae barrier. On the basis of studies with atractyloside, a compound inhibiting the exchange reaction, it is suggested that a specific translocase catalyses the exchange.

Utilization of high energy phosphate by the heart. About 60 to 70 per cent of the oxygen uptake of the normal myocardium performing mechanical work ceases when such work is stopped as by arrest[illegible] or fibrillation. This implies that this percentage or more of the high energy phosphate produced by oxidative phosphorylation is directed toward contractile purposes.[illegible] At first examination it would appear that CrP rather than ATP is the immediate energy source for contraction. Loss of CrP exceeds loss of ATP in several types of heart failure, including (1) that produced by asphyxiation of experimental animals,[illegible] (2) chronic heart failure produced by experimental pulmonary artery stenosis,[illegible] and (3) hereditary myocardiopathy of the Syrian hamster.[illegible] Furthermore, the loss and restoration of the mechanical power of the heart during oxygen-deprivation can be correlated with the CrP rather than the ATP concentration.[illegible] On the other hand, the following evidence links ATP utilization with contractility. First, in models of isolated skeletal myofibrils, development of tension can be correlated with the rate of mitochondrial regeneration of ATP.[illegible] Secondly, in isolated cultured rat heart cells blockage of ATP formation by oligomycin and iodoacetate stops the heart beat.[illegible] Thirdly, inhibition of oxidative phosphorylation by oligomycin in the isolated perfused rat heart leads to a diminished ATP content and decreased contractility.[illegible] Fourthly, in the frog rectus abdominus with ATP-CrP transfer blocked, the muscular work uses up ATP and the force of contraction decreases as the ATP concentration falls.[illegible]

Taken together, the above observations suggest that the ATP concentration in the myocardial cell is maintained at the expense of CrP, with CrP pool suffering depletion before ATP. This is in agreement with classical concepts of skeletal muscle physiology.

However, there is now evidence suggesting that CrP may act as a transit store of high-energy phosphate being transferred from one ATP compartment to another because failure can be produced in the rabbit heart-lung preparation by blockage of ATP-CrP transfer when levels of ATP and CrP are unchanged.[illegible]

Because a relatively small decrease in ATP concentration is associated with reduced myocardial contractility, it is possible that ATP used for contraction lies in a small compartment with a high turnover rate.

There is considerable controversy about the question of ATP usage in muscle relaxation. Using the frog muscle poisoned with fluorodinitrobenzene, Infante and Davies[illegible] report that ATP is broken down largely in the relaxation phase, whereas the detailed

studies of Mommaerts and Wallner[illegible] on a similar preparation suggest that all ATP breakdown occurs in the contraction phase. It should be noted that Davies theory of *muscular contraction* (see Section VIII) requires at least some ATP usage in relaxation If indeed Ca^{++} uptake by vesicles is the direct cause of muscle relaxation and this uptake is ATP-dependent then some ATP usage should occur in relaxation

That part of the oxygen uptake not used in the contractile process may be used in (1) ion transport across the cell membrane[illegible] (2) ion transport into and out of the mitochondrion[illegible] (3) energy-coupled changes in mitochondrial volume and structure (4) energy driven reversal of the electron transmitter chain[illegible] and (5) non phosphorylating cellular activities.[illegible] Some rough idea of ATP utilization in ion transport across the membrane of the resting heart cell can be derived by extrapolation from the brain where 40 per cent of the oxygen uptake is abolished when Na^+ transport ceases. In the heart the percentage of the oxygen uptake is associated with noncontractile metabolic activity may be about 35 per cent (see above) another estimate is 15 per cent.[illegible] If 40 per cent of the noncontractile activity be devoted to ion transport this corresponds to 14 per cent of the total myocardial oxygen uptake (using the higher estimate of noncontractile oxygen expenditure) It is of interest that the oligomycin-insensitive energy expenditure of the isolated rat heart is about 15 per cent of the total[illegible] this figure presumably includes energy expenditure on mitochondrial ion transport and mitochondrial contraction relaxation phenomenon[illegible] although the meaning of oligomycin insensitive respiration in the whole heart has not yet been elucidated

In summary extremely rough estimates would be that 60 to 70 per cent (or more) of myocardial energy expenditure is for contraction (and perhaps relaxation) about 15 per cent (or less) for that part of membrane ion transport not associated with contractile activity and the rest in mitochondrial functions such as ion transfer and contraction and relaxation phenomena and reversal of electron transport. In conducting tissue, a certain undetermined percentage of ATP usage may be concerned with maintenance of membrane action potential. No allowance has been made for ATP utilization in synthetic reactions which do occur in heart tissue (see Section VII) although to a lesser extent than in liver and kidney

Oxidative phosphorylation It is generally accepted that the rate of oxidative phosphorylation is coupled to the rate of electron transport in all tissues. Intact phosphorylating mitochondria require a phosphate acceptor[illegible] The concept of control of respiration by the intracellular ADP concentration has been discussed by Chance and Williams.[illegible] During oxidation of substrates yielding $NADH_2$ the phosphorylation oxygen (P/O) uptake ratio of isolated mitochondria is normally 3 higher ratios appear to have resulted from methodological errors. The P/O ratio has been extensively studied in isolated mitochondria and it is assumed but not proved that similar ratios hold in the whole organ. At present oxidative phosphorylation in the whole heart can only be studied indirectly for example by measuring the exchange rate between exogenous $^{32}P_i$ and myocardial pools of ATP ADP and P_i[illegible] or the exchange of ^{18}O with PO_4, as used in skeletal muscle.[illegible]

Muscular contraction by producing ADP[illegible] may be expected to play a major role in determining the rate of oxidative phosphorylation in the heart. When the force of contraction is increased by epinephrine, an increased oxygen uptake correlates with increased ADP formation[illegible] AMP which is also increased during epinephrine stimulation[illegible] may act as a phosphate acceptor in heart homogenates[illegible] but observations on isolated mitochrondria suggest that it is the endogenous ADP that is phosphorylated.[illegible] Thus, the AMP in the heart homogenates probably forms ADP via the adenylate kinase reaction before phosphorylation

Oxidative phosphorylation and high energy phosphates in heart failure Depressed rates of oxidative phosphorylation and a decreased content of ATP and/or CrP have been found in the myocardium in experimental heart failure produced by aortic or pulmonary constriction[illegible] or in spontaneously failing dog heart lung preparations.[illegible] In aortic constriction the defect in oxidative phosphorylation is localized to

the terminal part of the respiratory chain.[illegible] Furthermore, derangements of mitochondrial structure and enzyme activity and of oxidative phosphorylation occur early in the development of experimental left ventricular failure.[illegible] However, a decreased glycolytic rate accompanies a reduced oxygen uptake of the myocardium.[illegible] This implies a serious breakdown of the normal compensatory mechanism whereby the glycolytic rate increases in states of reduced oxidative metabolism and suggests that in these studies the heart tissue suffered from severe metabolic damage. However, a large number of other studies on acute and chronically failing hearts have found a normal concentration of high energy phosphate compounds as well as normal mitochondrial structure and unchanged capacity for oxidative phosphorylation.[illegible] Thus, changes in oxidative phosphorylation are inconstant and therefore not basic. Furthermore, even when the calculated capacity of mitochondria to synthesize high energy phosphates is reduced by half, normal mechanical performance can be maintained for months.[illegible]

Defective terminal chain oxidative phosphorylation and changes in high energy phosphate compounds have also been found in homogenates and mitochondria from a hereditary myocardiopathy in the Syrian hamster.[illegible] The oxygen uptake and the rate of glycolysis in slices from these hearts are increased, in keeping with a true uncoupling of oxidative phosphorylation. A parallel may exist between the changes found in hamster cardiopathy and in the heart disease of human muscular dystrophy in which a normal myocardial oxygen uptake is accompanied by an increased glucose extraction and an increased blood inorganic phosphate, which are only indirect evidence for uncoupled respiration.[illegible] Hamster dystrophy resembles some types of the human disease in the genetic pattern, in the histological changes and in an increase of serum CrP kinase.[illegible] Studies showing a metabolic defect in hamster cardiopathy may be more pertinent to human muscular dystrophy than to the much more usual type of failure following an increased mechanical load on the heart.

Two basic problems are inherent in all such studies. First, there is as yet no entirely satisfactory animal model corresponding to low output congestive heart failure in man. Secondly, there is difficulty in accurately assessing the rates of oxidative phosphorylation in vivo. Initial reports of measurements of the exchange of $^{32}P_i$ with myocardial ADP and Pi suggest that this line of approach will be fruitful.[illegible]

Mitochondrial metabolism: conclusions. Only a part of the total cellular ATP content appears to be available for contractile purposes, although about two-thirds or more of the myocardial ATP utilization is by the contractile process. This gives rise to the possibility that contraction ATP may lie in a small rapidly turning over compartment, quite probably in the cytoplasm. Cytoplasmic ATP can be replenished from mitochondrial ATP generated by oxidative phosphorylation through an exchange process thought to be regulated by a permease. The mitochondrial ATP content may autoregulate the rate of its production by inhibition of the initial steps of the citrate cycle.

The defects in oxidative phosphorylation described in some kinds of experimental heart failure do not appear to be primary lesions.

VII. Synthetic reactions in heart

Lipogenesis and ketogenesis. In the perfused rat heart, the rate of incorporation of ^{14}C from glucose or pyruvate into tissue fatty acids and other lipid fractions is very low.[illegible] On the other hand, mitochondria from the rabbit heart effectively catalyze the incorporation of acetate into long-chain fatty acids.[illegible] Furthermore, the possibility of extramitochondrial lipogenesis is raised by the occurrence of the citrate cleavage enzyme in hearts of several species.[illegible] The reason for the failure to demonstrate the activity of these fatty acid synthesizing systems in the whole contracting rat heart is not known. Possibilities include (1) a species difference, and (2) a limited rate of production of $NADH_2$ and $NADPH_2$, the sources of reducing hydrogen.[illegible] It has been suggested that mitochondrial fatty acid synthesis occurs especially during periods of restricted aerobic oxidation of $NADH_2$.[illegible] If this is so, the possibility is raised that at least some of the triglyceride accumulation in the heart in

ischemic states results from such mitochondrial synthesis.

Other possible limitations on the rate of fatty acid synthesis in heart mitochondria are (1) removal of malonyl CoA by transfer of CoA to succinate or by the activity of malonyl CoA decarboxylase,[334] and (2) inhibition of fatty acid synthesis from malonyl CoA by CoA, as in rat mammary gland mitochondria.[337]

The fatty acid synthesizing system of heart mitochondria is more effective for elongation and desaturation reactions from existing fatty acids than for synthesis of fatty acids de novo.[334] Also circulating long-chain FFA are readily incorporated by the isolated heart into various lipid fractions.[62,189,190] Thus the requirement for lipid in the heart for purposes other than respiration can theoretically be met by uptake of fatty acids of various chain lengths with appropriate reconstruction reactions within the heart cells.

The rate of formation of ketone bodies by the rat heart perfused with palmitate is low.[173] Ketogenesis from β-hydroxy-β-methylglutaryl CoA (HMG-CoA)[339] cannot occur in the heart because, although the HMG-CoA cleavage enzyme occurs in the heart,[340] the enzyme of HMG-CoA synthesis has not been found. An alternate pathway of ketogenesis is found in pig heart extracts.[341] Acetoacetate is formed from acetyl CoA with transfer of CoA to succinate and subsequent deacylation of succinyl CoA to regenerate succinate. However, to achieve ketogenesis in this preparation purified deacylase and a very high succinate concentration (50 mM.) are required. It would appear that pathways for ketogenesis are relatively unimportant in the whole heart.

Protein synthesis

SOURCE OF AMINOACIDS. Although the myocardial extraction of total aminoacid nitrogen from the circulation is normally very low,[171,217] there is uptake and release of individual aminoacids.[342] The importance of uptake of aminoacids for protein metabolism of the heart is shown by the decrease of protein content of the isolated heart when aminoacids are omitted from the perfusate.[343] Uptake of most aminoacids probably occurs against a gradient, because the intracellular content of "free" aminoacids in the normal heart exceeds the plasma concentration by several fold.[344] The relative roles of uptake from the circulation and transamination in the provision of alanine, aspartate, and glutamate in the heart are not known. However, small amounts of glucose carbon can be incorporated into alanine, glutamate, and protein in the isolated guinea pig heart.[297]

Besides utilization for protein synthesis, other possible fates of aminoacids in the heart are transamination and oxidation.[345,346] There is no reason to suppose that aminoacids are an important source of energy for the heart (Table IV).[171,260]

RIBOSOMAL AND MITOCHONDRIAL PROTEIN SYNTHESIS. When isolated perfused rat hearts are pulse-labelled with ^{14}C-aminoacids and then fractionated, the ribosomes are the most rapidly labelled cell fraction, suggesting that they are the active site of protein synthesis in the heart as in the liver. The properties of isolated ribosomes differ according to the method of preparation.[347-349] When the whole heart homogenate is treated by deoxycholate before differential centrifugation, heart ribosomes resemble those from the liver in the rate of incorporation of aminoacid into protein, the ion requirements, the stimulation by polyuridylic acid, and the inhibition by ribonuclease and puromycin.[349] There is some evidence that RNA from the rat heart muscle contains a heterogeneous, rapidly labelled fraction which may be messenger RNA.[270]

Heart mitochondria apparently freed from ribosomal contamination also incorporate aminoacids into protein by a process which is not inhibited by ribonuclease but by actinomycin D.[341] Such incorporation depends on the structural intactness of mitochondria and on their ability to carry out oxidative phosphorylation.[271] However, in the perfused heart, ^{14}C-aminoacids are incorporated much less into mitochondrial than into ribosomal protein. Presumably the ribosomal system of protein synthesis is used to manufacture contractile protein during cardiac hypertrophy, whereas the mitochondrial system more probably manufactures *structural proteins* and mitochondrial enzyme proteins.

EFFECT OF INSULIN. In the isolated rat heart, insulin stimulates the *intracellular*

accumulation of a nonutilizable aminoacid γ-aminoisobutyrate, and of proline and glycine.[373] Others find that there is no consistent effect of insulin on aminoacid uptake by the isolated heart but that there is intracellular accumulation of some aminoacids under the influence of insulin when protein synthesis is blocked by puromycin.[373] Insulin also stimulates the incorporation of aminoacid into protein in the perfused rat heart, while the addition of glucose causes a further stimulation for reasons not entirely clear.[373]

Protein synthesis by ribosomes from alloxan-diabetic heart muscle is decreased and the administration of insulin to the rat restores the ribosomal activity toward normal.[374] It does not, however, necessarily follow that there is decreased protein synthesis in the alloxan-diabetic heart in vivo because ribosomal activity has not been shown to be rate limiting for protein synthesis.

EFFECT OF GROWTH HORMONE. Cardiac ribosomes from hypophysectomized rats are unable to incorporate aminoacids into protein at normal rates, and are less able to react with polyuridylic acid to stimulate phenylalanine incorporation while the administration of growth hormone to the hypophysectomized animal remedies these defects.[31] However both growth hormone and insulin are required for optimal rates of incorporation of [14]C alanine into heart proteins of hypophysectomized animals.[375] Abnormal ribosomal function would explain why cardiac hypertrophy cannot occur in hypophysectomized rats after aortic constriction[57] but it must be pointed out that these animals do not develop hypertension as do similar rats treated with growth hormone or thyroid stimulating hormone; thus the stimulus to hypertrophy may be absent. Excess growth hormone can cause cardiac hypertrophy as in acromegaly or when repeated doses of growth hormone are given to rats.[377] It is suggested that cardiac hypertrophy can result either from hormonal stimulus in the presence of normal cardiac work or from increased cardiac work with normal hormonal production.[377] It should be noted that the presence of thyroid hormone is required for full response of the heart to growth hormone.[57, 377] Furthermore, growth hormone may chiefly influence size of the heart whereas thyroid hormone may control the maximal work producing capacity.[378]

EFFECT OF INCREASED HEART WORK. When the work of the isolated guinea pig heart is increased the rate of incorporation of aminoacid (as [14]C-lysine) into protein nearly doubles after 3 hours.[202] At the same time the total protein content decreases slightly which is evidence for an increased turnover of heart muscle protein during a work load. During the development of left ventricular hypertrophy in dogs with aortic stenosis there is initially increased incorporation of labelled aminoacid (as methionine) into myocardial protein.[15] Such increased protein synthesis requires an increase of DNA dependent synthesis of RNA.[379] If the aortic stenosis be maintained for months the heart ceases to enlarge further and the rate of protein synthesis reverts to normal; with the onset of chronic cardiac failure the rate of protein synthesis finally decreases.[15, 57]

The way in which increased cardiac work stimulates protein synthesis and cardiac hypertrophy is unknown. It is possible of course that increased cardiac work can cause increased protein synthesis by increasing aminoacid uptake. The uptake of some aminoacids by the heart resembles that of glucose in being insulin-sensitive and an active process. There may, therefore, be increased uptake of aminoacids across the cell membrane in response to increased cardiac work as there is increased glucose transport. Increased aminoacid uptake would result in increased intracellular aminoacid concentrations which may stimulate protein synthesis.[59]

Another possibility is an alteration in ribosomal activity. For example, acute overload of the isolated guinea pig heart stimulates microsomal protein synthesis.[181] Cardiac hypertrophy on the other hand is associated with an increased number of ribosomes.[31] It should be noted that messenger RNA could not be isolated in the latter study in contrast to another report.[379] In spite of such contradictions, it may be anticipated that studies along these lines will be rewarding.

Conclusions. The question of lipogenesis in the heart is raised by the finding of active mitochondrial synthetic systems, but it is not clear that these systems ever operate

in the heart in vivo except perhaps in ischemic states.

The regulation of protein synthesis is still poorly understood. It appears that cardiac ribosomes synthesize proteins from aminoacids probably derived from the circulation and that such synthesis is influenced by insulin, growth hormone and thyroid hormone. The mechanism of increased protein synthesis during increased cardiac work is unknown. Possibilities include (1) increased transfer of aminoacids across the cell membranes, and (2) an increased protein synthesis by ribosomes.

VIII The conducting system, excitation—contraction coupling and cardiac contraction

Metabolism of the conducting system. The conducting system has properties which largely differ from those of mature heart muscle, and more closely resembles embryonic myocardium[illegible] and therefore, white muscle (Section V). Conducting tissue may depend more on glycolysis for its energy supply than does the rest of the myocardium because the oxygen uptake and the activity of succinate dehydrogenase are much lower in conducting tissue whereas the glycogen concentration is higher and the capacity to survive anoxia is greater. Connective tissue has a high content of both monoamine oxidase and of cholinesterase.[illegible] Müller and Pearse[illegible] suggest that the cholinesterase activity is concerned with the response to cholinergic stimuli while the monoamine oxidase activity in the tissue surrounding the conducting cells, protects the conducting system from catecholamines (see Section VIII for comments on the role of monoamine oxidase).

Calcium flux and excitation-coupling. The indispensable role of calcium in maintaining the force of cardiac contraction has been accepted since the observations of Ringer.[illegible] At low external calcium concentrations there is decreased cardiac contractility. Conversely, increased calcium results in increased tension development and splitting of ATP in isolated rabbit atria[illegible] there is also a lowered ventricular filling pressure and an increased rate of tension development and relaxation in the dog heart lung preparation.[illegible] The amount of calcium influx per beat is very low being about 10^{-7} moles in a 80 mg frog heart.[illegible] Calcium is also required for contraction of glycerinated muscle fibers, for superprecipitation of myofibrils and of actinomyosin (at physiological ATP concentrations) and for maximum activity of the magnesium-activated myofibrillar ATPase.[illegible]

Calcium flux in the heart has been defined by studies using[illegible] Ca. The major component of calcium flux is independent of cardiac contraction, it can be subdivided into a rapidly exchangeable phase of half-life of 4 to 6 minutes and a much slower component merging into a nonexchangeable calcium fraction.[illegible] A second component of calcium flux depends on cardiac contraction and is increased by the heart beat. Increased influx is associated with unchanged total tissue calcium suggesting that calcium efflux is also stimulated by contraction.[illegible]

Uptake of calcium into the sarcoplasmic vesicles appears to be important for the relaxation of both skeletal and heart muscle. The activity of the relaxing factor which causes relaxation of contracted myofibrils,[illegible] can be explained by the action of vesicles in concentrating the calcium ion 1 400 to 5 000 times by means of a pump which takes up 1 or 2 moles of calcium per mole of extra ATP split.[illegible] It is suggested that calcium influx is accelerated by a globulin transport system which is increased in the plasma of patients with essential hypertension and severe aortic stenosis.[illegible] So far there appear to be no attempts to duplicate this work.

The relation between contraction and calcium influx may explain the increased contractility during tachycardia or paired stimulation in the isolated rat heart.[illegible] Calcium flux may compete with sodium for a common carrier in the heart[illegible] and as for sodium there may be an active pump for extrusion of the ion from the muscle cell.[illegible]

Intracellular calcium is thought to exist in 2 interacting forms, activator-calcium which induces the contraction and a larger store of inactive calcium.[illegible] The amounts of activator-calcium involved are minute. A threshold concentration of ionized calcium of 0.3 to 1.5 μM is required to cause contraction of crab muscle fibers,[illegible] while about 0.1 mM calcium saturates isolated actomyosin.[illegible] Activator-calcium is thought

to be located in a superficial part of the cell such as the membrane or the sarcoplasmic reticulum.[illegible] In skeletal muscle activator-calcium is thought to be released from the tubules of the sarcoplasmic reticulum. Autoradiographic studies show that, as skeletal muscle is activated, calcium ions move from the area of the Z-band (where the tubular system is located) to the A band.[illegible] A similar tubular system is seen in cardiac muscle[illegible] and cardiac sarcoplasmic vesicles may release calcium during electrical stimulation.[illegible] An alternate source of activator-calcium is that calcium entering the cell membrane during excitation.[illegible]

The uptake of calcium by the sarcoplasmic reticulum from the heart might inhibit the contraction of myofibrils,[illegible] by lowering the free calcium ion concentration below a critical level (10^{-7} M). In certain conditions the degree of relaxation induced is related to the amount of uptake of calcium.[illegible]

The intimate relationship between the amount of ionized calcium available to the contractile system and the state of contraction or relaxation is stressed by Nayler.[illegible]

Calcium and pathological states. Evidence for a possible role of calcium in heart failure is as follows. Heart failure can be produced by perfusion of hearts with cobalt or nickel ions, which mimic the metabolic and mechanical effects of calcium deficiency presumably by interfering with the role of calcium ions in excitation-coupling.[illegible] Heart failure produced by poisoning with barbiturates, some local anesthetics, or β-blockade is also thought to depend on interference with the role of calcium in contraction because the addition of calcium reverses the failure.[illegible] In the guinea pig heart lung preparation congestive cardiac failure can be produced by high doses of dichloroisoproterenol (a catecholamine analogue) and reversed by the addition of calcium ions.[illegible] These observations may be related to the effect of catecholamine analogues in decreasing the utilization of calcium ions by cardiac myosin B.[illegible] Furthermore, the sarcoplasmic vesicles derived from the spontaneously failing dog heart lung preparation have decreased in vitro uptake of calcium ions, and this defect is reversed by ouabain.[illegible] Thus, an important investigation would be to measure calcium uptake by vesicles from humans with congestive heart failure; material for such studies may become available as heart transplants become more common.

The calcium-paradox recently described by Zimmerman and co-workers[illegible] draws attention to an important phenomenon. If the isolated perfused rat heart is arrested by a calcium free solution, the reintroduction of calcium causes extensive damage to myocardial cells and to vessel walls. The inference is that there is real danger in inducing cardiac arrest by low calcium-ion solutions.

Finally, decreased calcium uptake by sarcoplasmic vesicles may play a role in cardiac arrest following prolonged anoxia.[illegible]

Molecular events during contraction. The following brief survey should be supplemented by reference to Gergely's review on the contractile proteins.[illegible] Muscular contraction occurs as an interaction between actin and myosin. According to Huxley's classic sliding model,[illegible] the thin actin filaments interdigitate with the thick myosin filaments, and during contraction they slide between the myosin strands. Previous evidence for a folding model has not been substantiated.[illegible] Myosin has 2 subunits. Light or L-meromyosin is rodlike and without ATPase activity.[illegible] Heavy or H meromyosin complexes with ATP and forms the myosin cross-bridges to the actin filaments.[illegible] The ATPase activity of skeletal myofibrils is localized to the area in which thick and thin filaments overlap,[illegible] and histochemical studies in the rat heart suggest that the activity of this ATPase is located at the cross-bridges.[illegible] Actin in the fibrous form is composed of a two-stranded helix of 13 globular subunits per twist of helix.[illegible] The exact conformation of the molecule may be influenced by interaction with ATP and metal ions at several sites.[illegible]

Cardiac and skeletal muscle myosin resemble each other in their microanatomy[illegible] and in many molecular properties[illegible] although cardiac myosin has a lower ATPase activity and there are differences in the fine molecular structure near the enzyme site.[illegible] Although the amount of sarcoplasmic reticulum is less in cardiac than in skeletal muscle, the rate of calcium uptake

by isolated sarcoplasmic reticulum is about the same.[illegible]

Evidence linking ATP to contractility of the heart has already been reviewed in Section VI. It is also pertinent to note that ATP causes the contraction of threads formed by the combination of actin and myosin[illegible] and those actomyosin bands prepared from human hearts contract in the presence of ATP.[illegible] As previously discussed, any ATP usage during muscular contraction probably reflects energy required to allow Ca^{++} uptake by the sarcoplasmic vesicles.[illegible]

Davies[illegible] has postulated that calcium might trigger contractions as follows. ATP located at the tip of the H meromyosin side-chain may keep the side-chain extended by electronegative charges. When calcium ions arrive locally, they form a chelating link (with the ATP) between actin and the myosin side-chains. The calcium-ATP bond neutralizes the electronegative charges on the side-chain, which therefore contracts and pulls the ATP toward the ATPase (at the base of the side chain). ATP is hydrolyzed and the calcium-ATP bond is disrupted. As ATP reforms the electronegative charges are again generated and the side-chains re-extend. These cyclical changes are repeated when calcium again binds to the reformed ATP. It is not yet clear how newly-described protein components sensitizing actomyosin to calcium[illegible] would fit into this scheme.

Another suggested explanation of the interaction between ATP and calcium is that a high concentration of ATP as the ATP Mg moiety inhibits contraction of actomyosin and that calcium overcomes this inhibition.[illegible] ATP may either cause dissociation of actomyosin or act by substrate inhibition to decrease ATPase activity. This hypothesis would explain the requirement for calcium only at higher ATP concentrations (exceeding 10 μM).[illegible] If multiple sites participate in superprecipitation,[illegible] a complex interaction between calcium and ATP inhibition can be anticipated.

Contractile proteins in heart failure. Structural abnormalities of the contractile proteins have been found in both animal and human heart failure.[illegible] Olson[illegible] found that myosin from failing hearts had a molecular weight 3 times that of normal myosin, but this conflicted with the findings of others[illegible] and could not be confirmed by Olson on reinvestigation.[illegible] A major problem in the interpretation of protein studies is that the methods involved are complex. Furthermore, even if changes are found, they could as readily result from as be the cause of myocardial failure. For example, stretching of the sarcomeres as a result of congestive failure[illegible] would result in decreased ATPase activity,[illegible] which would explain the decreased ATPase activity found in muscle from failed hearts.[illegible] Mommaerts and Langer[illegible] have, therefore, pleaded for a decisive reinvestigation into the possible role of the contractile proteins in heart failure.

Conclusions. Calcium movements play an indispensable role in contraction and relaxation of the actomyosin system in the heart. Interference with this role may be found in some types of experimental heart failure. It has also been suggested that there may be defects in the contractile proteins in congestive heart failure, but there are many technical problems in the execution and interpretation of such studies.

IX. Catecholamines

Synthesis of catecholamines by the heart. Norepinephrine is synthesized in the isolated mammalian heart from tyrosine via dopa and dopamine.[illegible] The major part of myocardial norepinephrine appears to be synthesized within the heart.[illegible]

The enzymes involved in norepinephrine synthesis are *tyrosine hydroxylase, aromatic amino-acid decarboxylase* and dopamine-β-oxidase.[illegible] The rate-limiting enzyme for norepinephrine synthesis in the heart is tyrosine hydroxylase.[illegible] Inhibition of tyrosine hydroxylase by injection of α-methyl tyrosine into the guinea pig reduces the catecholamine content of the heart.[illegible]

The location of the norepinephrine-synthesizing enzymes in the cell is not fully known. Wurtman[illegible] reviewed evidence for the localization of tyrosine hydroxylase in mitochondria, the decarboxylase in the cytoplasm, and dopamine-β-oxidase in the norepinephrine storage granules, and he postulated movements of substrates from one intracellular locus to another during norepinephrine synthesis. Udenfriend[illegible] has

suggested a simpler scheme, whereby all 3 enzymes are organized into one organelle which may be the storage granule.

Uptake of catecholamines by the heart. Because of the virtual absence of the appropriate myocardial enzyme, epinephrine cannot be synthesized and the epinephrine found in the heart is taken up from the circulation.[illegible] By contrast, only part of myocardial norepinephrine originates from the circulation,[illegible] but this part may be more physiologically active than endogenously synthesized norepinephrine.[illegible]

The mechanisms controlling catecholamine uptake by the heart participate in the regulation of myocardial catecholamine levels. Catecholamines can be taken up by heart slices both by diffusion and by a concentrating mechanism; the latter is inhibited by reserpine and ouabain and is saturated by 25 mμg per milliliter of norepinephrine.[illegible] In the perfused rat heart, both catecholamines are accumulated against a gradient in competition with each other by a process which obeys Michaelis-Menten kinetics, and is favorable to (−) isomers.[illegible] The Km values appear to be 100 to 1 000 times lower than the circulating catecholamine concentrations of resting humans. However, such information could only be appreciated fully if Km values for catecholamine uptake could be compared with circulating blood catecholamine concentrations, of the same species, under both basal and stressed conditions.

Localization of catecholamines in the heart. Anatomically, the catecholamines are found in small (30 to 60 mμ) granulated vesicles in the preterminal sympathetic fibers,[illegible] which separate out in the microsomal layer on sucrose gradient ultracentrifugation.[illegible] Norepinephrine can be concentrated 35 times in these particles; it is stored in a stable complex with ATP, and it is released by hypotonic solutions, reserpine, and tyramine. The relative absence of enzymes inactivated catecholamines from these particles suggests that further metabolism of norepinephrine may occur only after release from the storage particles.

There are several functional compartments or pools of catecholamines in the heart and other tissues.[illegible] It is suggested that tissue ³H-norepinephrine can be found within the sympathetic nerve endings in 2 pools distinguished by their response to tyramine.[illegible] However, the use of tyramine to distinguish such pools is now suspect because the extent of tyramine caused depletion is markedly dependent on the scheme of administration of the dose,[illegible] and because 80 to 90 per cent of the rat heart norepinephrine can be depleted rapidly by large doses of tyramine.[illegible] Nevertheless, the concept of pools of varying turnover rates remains useful in explaining differences between the total catechol amine content of the heart and the metabolically active fractions.

Free catecholamine derived either from the rapidly turning-over pool of the storage particles or from the circulation may become active in combination with receptor sites. α- and β-receptors are postulated to explain studies with blocking agents. Nethalide, a β-blocker, prevents the inotropic and chronotropic actions of catecholamines,[illegible] as well as the formation of cyclic AMP and the activation of phosphorylase.[illegible] Thus, there is evidence that both mechanical and metabolic effects of catecholamines are mediated through β-receptors.

Free catecholamine that has not interacted with β-receptors may be removed by (1) rebinding with cardiac sympathetic nerves,[illegible] or (2) loss into the circulation, or (3) 0-methylation.[illegible] The latter fate is relatively unimportant in the heart of the rat (but not necessarily of other species).[illegible] It should be noted that monoamine oxidase apparently only inactivates catecholamine in the slowly turning-over tissue pool located in the nerve endings.[illegible]

Release of catecholamine by the heart. Release of catecholamine from the heart into the circulation may occur after the administration of vasoactive amines,[illegible] after stimulation of cardiac sympathetic nerves,[illegible] or when the left ventricle develops increased systolic pressure.[illegible] Anoxia releases about one-quarter of the norepinephrine stores of the isolated rabbit heart; the fraction released appears to correspond to the tyramine-sensitive pool.[illegible] Because of the capacity of the heart to synthesize store and release norepinephrine, it has been suggested that the heart is a neuroendocrine organ.[illegible]

Inotropic effect of catecholamines. Evi

dence for the role of cardiac β-receptors in the action of catecholamines has already been reviewed. There are currently 2 main theories to explain the inotropic effects of the catecholamine receptor complex. (The possibility of a primary effect of catecholamines on the cardiac phosphorylase system is no longer acceptable, as discussed later.) First, the adenyl cyclase system may be the tissue receptor.[illegible] It is suggested that production of cyclic AMP by this system may lead to stimulation of both the phosphorylase system (see Section II) and to the inotropic effect. There is, however, scant evidence that cyclic AMP is inotropic. The finding that the cardiac output rises when cyclic AMP is infused into humans[477] could mean that cyclic AMP increases the force of cardiac contraction after crossing the cell membrane but it is difficult to exclude an effect of cyclic AMP on the cell membrane (e.g., a change in permeability to calcium). Although stimulation of the isolated rat heart by epinephrine causes the cyclic AMP level to rise before the inotropic effect occurs, yet the cyclic AMP level returns to normal while the force of contraction remains increased.[illegible] Furthermore, in isolated organelles (myofibrils and myosin B) catecholamines but not cyclic AMP can be shown to have an inotropic effect.[47]

For these reasons, an alternate theory is more acceptable at present. When myofibril gels are prepared in such a way that they respond directly to catecholamines, the stimulant effect is blocked by equimolar analogues such as dichloroisoproterenol; the characteristics of the blockade are similar to those of adrenergic blockade in vivo.[47] The effect of analogues in delaying superprecipitation of myosin B is reversed by catecholamine or calcium in high concentrations.[47] It is therefore possible that catecholamines promote the tension-generating chelate linkage of myosin to actin and that this action is co-catalytic with that of calcium. Thus, it is proposed that the receptor site is on the myofibril, perhaps on myosin B.[47] According to this interpretation, the metabolic effects of catecholamines (especially on glycogenolysis and glycolysis) are largely secondary to the inotropic effect. It should be noted that a location of β-receptor sites in the myofibril implies a basic difference between the nature of the tissue receptor in the muscle and other tissues. This second hypothesis is not negated by the finding that catecholamines do not influence ATPase activity of cardiac myosin or reconstituted actomyosin.[illegible] However, more data is required to clarify fully the interaction between catecholamines and the contractile process.

Effect on oxygen uptake. Increased qO_2 produced by catecholamines in the beating heart is largely due to the increased contractile activity.[illegible] There is also a direct stimulation of oxidative metabolism detected even in the K^+-arrested heart and attributed to release of FFA within the heart from triglyceride stores; subsequent oxidation of FFA increases the qO_2 by an unknown mechanism.[illegible] A report that norepinephrine does not increase the qO_2 of the human heart, despite increased arterial pressure and time tension index,[illegible] is difficult to evaluate without full hemodynamic data such as the left ventricular end-diastolic volume and the velocity of contraction, which determine the myocardial metabolic response to sympathomimetic agents and catecholamines.[474,477]

Effects on carbohydrate and lipid metabolism. Catecholamines influence the metabolism of endogenous myocardial lipid. Sympathetic denervation of the canine heart results in an increased myocardial level of total and esterified fatty acids.[47] Conversely, catecholamines stimulate turnover of endogenous triglycerides in both the K^+ arrested and the beating perfused rat heart, and lipolysis is reflected in enhanced glycerol release from the heart.[illegible] It would be of great interest to know whether catecholamine-stimulated lipolysis in the heart is mediated by cyclic AMP as suggested for adipose tissue.[illegible]

In isolated hearts perfused with glucose as the sole substrate, glycolysis increases following epinephrine stimulation[illegible] through activation of phosphofructokinase.[illegible] When humans are subjected to infusions of norepinephrine, there is evidence for decreased rather than increased glycolysis in the heart, together with a greatly increased uptake and oxidation of FFA.[illegible] Output, instead of uptake, of pyruvate by the heart suggests that glycolysis is restricted by enhanced FFA metabo-

ism.[illegible] In dogs FFA uptake and oxidation also increase following increased circulating concentrations during an intravenous infusion of norepinephrine, while a decreased respiratory quotient suggests decreased glucose utilization.[illegible]

Even when the concentration of FFA reaching the heart is kept constant, the effects of catecholamines on myocardial metabolism appear to vary. In the isolated rabbit heart perfused with albumin bound FFA as the only substrate, palmitate oxidation increases by 50 per cent during an infusion of epinephrine or norepinephrine.[illegible] However, in the isolated rat heart perfused with both glucose and palmitate as substrates, the rate of palmitate oxidation decreases when epinephrine is added to the perfusate; furthermore, uptake and oxidation of glucose and production of lactate are increased, showing that glycolysis is stimulated at the expense of FFA metabolism.[illegible] Similarly, an infusion of epinephrine into the left coronary artery of the dog results in decreased FFA extraction and oxidation while production of lactate suggests that glycolysis is stimulated to exceed the oxidative capacity of the citrate cycle.[illegible] However, no lactate production occurs during a similar infusion of norepinephrine.[illegible]

Thus, the rate of glycolysis may either decrease or increase in hearts exposed to epinephrine. This conflict can be resolved by accepting that the primary role of catecholamines is in stimulation of glycolysis as in the isolated heart perfused with glucose and FFA, and in the dog heart during an intracoronary infusion of epinephrine. However, when the rate of glycolysis is limited by the absence of glucose from the perfusate or when the circulating FFA concentration rises following an intravenous infusion of catecholamines, then oxidation of FFA increases at the expense of glycolysis. This interpretation is complicated by the unexplained failure of intracoronary norepinephrine (as opposed to epinephrine) to stimulate glycolysis in the dog heart.[illegible]

Interrelationships of inotropic and metabolic effects. Findings favoring a relationship between the inotropic effect of catecholamines and the stimulation of phosphorylase activity and glycolycogenolysis, have been reviewed by Haugaard and Hess.[illegible] In both the Langendorff heart preparation[illegible] and the open-chest dog preparation[illegible] catecholamine stimulation appears to increase phosphorylase activity pari passu with the inotropic effect. Inotropic and enzyme effects are closely correlated during stimulation by a variety of sympathomimetic amines and during cardiac sympathetic nerve stimulation.[illegible] Such data suggested to Haugaard[illegible] that the catecholamine mediated breakdown of glycogen could be important in the control of myocardial contractility.

Objections to the hypothesis linking phosphorylase activation with the positive inotropic effect of catecholamines are many and include the following. First, the inotropic effect is not always related to the concentration of active phosphorylase.[illegible] Secondly, in the isolated perfused rabbit heart the percentage of phosphorylase *a* increases concurrently with increased myocardial cyclic AMP but without a fall in cardiac glycogen within 30 seconds of exposure to catecholamine.[illegible] Thirdly, the inotropic effect on the dog heart in situ can be elicited by doses of catecholamines too low to activate phosphorylase.[illegible] Fourthly, in kinetic studies on the working isolated perfused rat heart exposed to epinephrine, the myocardial concentration of cyclic AMP rises within seconds, to precede the inotropic effect; phosphorylase *b* kinase is then activated and lastly phosphorylase is also activated about 20 seconds after the epinephrine stimulus.[illegible] Fifthly, the accumulation of glucose phosphates during the period of increased glycogenolysis[illegible] suggests that some step between G-6-P and lactate is rate-limiting; hence, an alteration in the rate of glycogenolysis is unlikely by itself to be an effective means of regulating glycolysis.

Thus, there is much evidence against accepting hypotheses linking the rate of glycogenolysis to cardiac contractility. Nevertheless, there must be a close relationship between the over-all rate of provision of substrate for oxidative purposes and the inotropic effect of catecholamines, perhaps as follows. ATP breakdown associated with or following the inotropic effect of catecholamine stimulation would result

in increased cellular concentrations of AMP Pi and cyclic AMP activation of myocardial phosphorylase, phosphofructokinase and lipase would follow with increased rates of glycogenolysis, glycolysis and lipolysis. Hereby increased breakdown of carbohydrate *and* lipid substrates would lead to a restoration of the ATP concentration

Catecholamines and antiadrenergic drugs in heart failure. The catecholamine content of the heart is depleted in both experimental and human congestive heart failure.[illegible] The decreased norepinephrine content in severe heart failure may be related to decreased uptake of norepinephrine.[illegible] There is no simple relationship between catecholamine depletion and impaired mechanical function of the heart,[illegible] which suggest that the depletion is not a basic and primary event in heart failure. These findings do, however argue strongly against the use of antiadrenergic drugs in patients with established heart failure. Furthermore, antiadrenergic drugs interfere with the compensatory role of the adrenergic nervous system in maintaining circulatory adjustments to heart failure.[illegible]

Conclusions Catecholamines, taken up from the circulation or synthesized in the heart, play an important role in the regulation of contractility oxidative metabolism, and glycolysis in the heart. The possible molecular events involved in these actions are reviewed in detail. In heart failure, the myocardium becomes depleted of catecholamines, which argues against the use of antiadrenergic drugs in this situation.

Fundamentals of clinical cardiology

Conduction disturbances before and after surgical closure of ventricular septal defect

H. E. Kulbertus, M.D.
J. J. Coyne, M.D.**
K. A. Hallidie-Smith, M.B., M.R.C.P.
London, England

The electrocardiographic association of right bundle branch block with left axis deviation of the mid vector (30 to 60 milliseconds, superior to −30° and of counterclockwise rotation in the frontal plane) was originally considered to be pathognomonic of an endocardial cushion defect.[1-3] However the same pattern has been recently reported in other congenital anomalies, such as ostium secundum atrial septal defect, ventricular septal defect,[4-7] double outlet right ventricle, multiple muscular ventricular septal defects,[11] cor triloculare biventriculare,[12] or congenital aneurysm of the membranous septum.[13]

The same electrocardiographic association has also been observed in atherosclerotic heart disease[14-17] and myocarditis,[1,3] and has been considered since 1956 to be due to a bilateral conduction abnormality.[1-3] Left axis deviation is thought to be due to a block of the superior division of the left bundle branch, and atrioventricular excitation depends primarily on the conduction in the inferior division of the left bundle branch. This condition is frequently complicated by complete atrioventricular block.[13]

The purpose of this paper is to report the conduction abnormalities observed electrocardiographically before and after surgical closure of ventricular septal defects with special reference to the incidence, causes, and potential hazards of the association of right bundle branch block with left axis deviation of the mid vector.

Patients and methods

The present series consists of 282 patients with ventricular septal defect who were investigated and operated upon at the Royal Postgraduate Medical School since 1959. There were 159 male patients and 123 female patients, ranging in age from 18 months to 45 years.

The ventricular septal defect was an isolated lesion in 140 patients (79 male, 61 female), part of the tetralogy of Fallot in 136 patients (77 male, 59 female), and

From the Department of Medicine (Clinical Cardiology), Royal Postgraduate Medical School and Hammersmith Hospital, London, England.
*Aspirant du Fonds National Belge de la Recherche Scientifique. Present address: Division of Cardiology, Department of Medical Clinic and Semeiology, University of Liège, Belgium.
**Supported by a grant from the New York Academy of Medicine, and the John C. Sable Heart Fund, Inc., Rochester, N.Y.

part of a common atrioventricular canal in 6 patients (3 male, 3 female)

The following electrocardiographic criteria were used Lone left deviation of the mean QRS axis was diagnosed when the QRS axis was −30° or superior According to the classical concept, complete right bundle branch block was present when the QRS duration was 0 12 sec. or longer and when the intrinsicoid deflection was delayed in the right precordial leads to 0 09 sec. or more. In the presence of right bundle branch conduction abnormalities, the QRS complex was assessed according to a trivectorial analysis.[29] From measurements made on scalar tracings the three main activation vectors were projected onto the hexaxial frontal plane lead reference system. The angular direction of each vector was measured with accuracy to 15°

Left axis deviation of the second vector was diagnosed when this vector was −30° or superior (Fig 1) regardless of the mean QRS axis. This last point is stressed since left axis deviation of the second vector was sometimes recognized in cases where the mean QRS axis was to the right (Fig. 2).

Results

The conduction abnormalities disclosed before and after surgery are set out in Table I

Tables II and III summarize the hemodynamic and surgical findings in the 6 patients with left deviation of the mean QRS axis and in the 15 patients with ventricular septal defect or tetralogy of Fallot who prior to surgery had an atrioventricular canal type of electrocardiogram.

Seven patients had a very large ventricu-

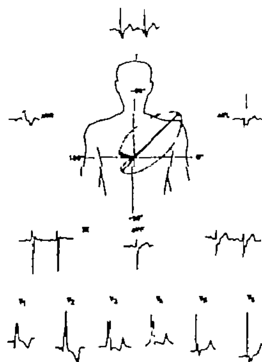


Fig 1 Electrocardiogram and individual vector orientation in a patient (Case 1) with an endocardial cushion defect. The left axis deviation of the second vector and the rightward direction of the third vector are well shown.

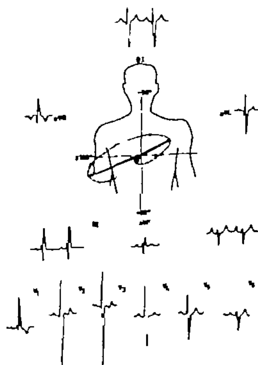


Fig 2 Electrocardiogram and individual vector orientation in patient (Case 2) with the tetralogy of Fallot who had an endocardial cushion type of ventricular septal defect. The mean QRS axis is deviated to the right but the left axis deviation of the second vector is still well seen.

Table I

	Conduction abnormalities before surgery			Conduction abnormalities acquired at surgery		
	L.A.D. alone	*R.B.B.B. alone*	*L.A.D. and R.B.B.B.*	*L.A.D. alone*	*R.B.B.B. alone*	*L.A.D. and R.B.B.B.*
Ventricular septal defects (140 patients)	3 2.1%	4 2.8%	8 5.7%	1 0.7%	98 75%	14 10%
Tetralogy of Fallot (136 patients)	3 2.2%	5 3.7	7 5.2%	—	64 49%	10 7.7%
Complete atrioventricular canal (6 patients)	—	—	6 100%	—	—	—
Total	6 2.1%	9 3.2%	21 7.2%	1 0.35%	162 59%	24 8.7%

*L.A.D., left axis deviation; R.B.B.B., right bundle branch block.

Table II Left axis deviation of the mean QRS axis

	Age	*Sex*	*Diagnosis*	*Surgical findings*	*Systemic arterial pressure (mm. Hg)*	*Systolic right ventricular pressure (mm. Hg)*	*Pulmonary-to-systemic flow ratio*
1	7	M	V.S.D.	Lack of septum. Hemipericardium	88	70	2.0
	21	M	V.S.D.	Infracristal VSD (5 by 3 cm.) with double outlet right ventricle	110	94	2.4
3	7	F	V.S.D.	VSD (outflow tract) (1.5 by 1.5 cm.) and 1 by 1 cm. muscular VSD	91	85	2.8
4	3	M	Tetralogy of Fallot	Infracristal VSD (2.5 by 2.5 cm.); small VSD located under the septal cusp of tricuspid valve; small secundum ASD; aorta-right coronary fistula; sinus of Valsalva ruptured into right ventricle	90	90	1
	9	F	Tetralogy of Fallot	2 medium-sized VSD* (fibrous and muscular septum); multiple muscular VSD; grossly abnormal tricuspid valve and papillary muscle	110	107	1
6	9	F	Tetralogy of Fallot	Infracristal ventricular septal defect (2 by 6 cm.)	75	85	0.7

*VSD, ventricular septal defect; ASD, atrial septal defect.

Table III *Left axis deviation of the second vector and right bundle branch block*

Age	*Sex*	*Diagnosis*	*Surgical findings*	*Systemic arterial pressure (mm. Hg)*	*Systolic right ventricular pressure (mm Hg)*	*Pulmonary-to-systemic flow ratio*
9	M	V S.D	Complete lack of septum	85	90	2 5
14	F	V.S.D	Endocardial cushion defect (0.5 by 0.5 cm.). Trivial aortic incompetence	108	28	2 4
6	F	V.S D	Endocardial cushion defect (1 by 1 cm)	76	34	1 9
6	M	V.S.D	Endocardial cushion defect (1 by 1.5 cm.)	85	47	1 7
10	M	V.S D	Endocardial cushion defect (1.5 by 1 5 cm.)	77	35	2
7	F	V.S.D	Infracristal VSD (1.5 by 2 cm.) associated with membranous septal defect	85	70	2 2
28	M	V.S.D	Infracristal VSD (1 by 0.5 cm.) with prolapsed right coronary cusp and considerable aortic regurgitation	108	23	7
3	F	V.S.D	Infracristal VSD (2.5 by 1 cm)	77	35	2
9	F	Fallot	Infracristal VSD (2 by 6 cm.)	95	85	0 7
10	F	Fallot	VSD (4 by 3 cm) with severe pulmonary stenosis	128	122	0 3
11	M	Fallot	Endocardial cushion defect	95	100	1 2
12	F (mongol)	Fallot	*Infracristal VSD (3 by 3 cm.)*	*120*	*110*	*1*
7	MO	Fallot	Endocardial type of VSD (2.5 by 2.5 cm.) with communication between LV and RA and cleft *leaflet of the tricuspid valve*	110	112	1 1
14	F	Fallot	Infracristal VSD (2.5 by 2.5 cm.) associated with 4 muscular VSD'	100	100	1
7	F	Fallot	Infracristal VSD (1 6 by 2 cm.) associated with m ltiple muscular VSD'	85	75	2 1

*V.S.D ventricular septal defect, R.A., right atrium L.V left ventricle

lar septal defect or incomplete common ventricle 7 patients had an endocardial cushion type of ventricular septal defect 5 patients had an infracristal ventricular septal defect associated with muscular defects and one patient had a prolapsed right coronary cusp and aortic regurgitation. In only one case the defect was described by the surgeon as a moderate sized infracristal ventricular septal defect.

Nine patients (4 with a ventricular septal defect 3 with the tetralogy of Fallot and 2 with a complete atrioventricular canal defect) died at operation or soon after surgery and had no postoperative electrocardiogram recorded

Left axis deviation alone appeared after surgery in only one patient who had an infracristal ventricular septal defect and developed an anteroseptal infarction following a difficult coronary perfusion. The axis shift was due to a left superior peri-infarction block.

Twenty four patients developed right bundle branch block and left axis deviation of the second vector after surgery One of them had an endocardial cushion type of ventricular septal defect, but did not

exhibit preoperatively the characteristic electrocardiogram In another there was a communication between the left ventricle and the right atrium. In the 22 others, the ventricular septal defect was infracristal uncomplicated and moderate in size (less than 25 mm. in the largest diameter)

Episodes of complete heart block were encountered in 24 patients (8.7 per cent) of whom 11 died. Fifteen had the tetralogy of Fallot, 5 had a ventricular septal defect and 4 had a complete atrioventricular canal defect. The QRS morphology was analyzed during periods of supraventricular conduction. Three of these patients showed a right bundle branch block which had appeared after surgery Eleven had congenital or postsurgical right bundle branch block pattern with left axis deviation of the mid vector All 4 patients with a complete atrioventricular canal who survived surgery had episodes of complete heart block for short periods following the operation

Discussion

As a result of differences in the criteria for left deviation of the mean QRS axis, the incidence of this feature in our cases (2.1 per cent) is not comparable with that observed in other series.[22-23]

Left axis deviation of the mid vector and right bundle branch block was not an uncommon association We have noted it in 7.2 per cent of our cases which corroborates other series (8 per cent[7] 15 per cent,[6] 4.2 per cent, 6 4 per cent, and 8 9 per cent in autopsied cases of tetralogy of Fallot and ventricular septal defect respectively[4])

From our observations and from the literature, it appears that left deviation of the mean QRS axis, as well as right bundle branch block, and left axis deviation of the mid vector seem to be related to unusual varieties of ventricular septal defects such as a very large defect or in complete single ventricle, endocardial cushion type of ventricular septal defect,[4] multiple muscular defects, double outlet right ventricle or ventricular septal defect with aortic regurgitation However they have been observed in patients whose defect was described by the surgeon as the usual type of small ventricular septal defect (case 14 of this series) [7]

The etiology of the association of right bundle branch block pattern with left axis deviation of the mid vector observed preoperatively is not clear Left axis deviation seems best explained by an abnormal distribution of the specific conducting tissue. Feldt and associates[8] have recently studied the morphology of the atrioventricular conduction system in a few cases of ventricular septal defect and tetralogy of Fallot who had a frontal plane vectorcardiogram similar to that usually found in a case of atrioventricular canal. They found that the distance between the atrioventricular node and the origin of the left bundle branch was consistently shorter than usually found This had also been observed in atrioventricular canal[23] where the left bundle bifurcates very early and gives off immediately an inferior division which descends abruptly to the apex and supplies a few fibers to the posterobasal area of the septal wall.

This anatomical situation appears to predispose to relatively early conduction to the posterobasal area of the left ventricle.[8] Recently epicardial recordings[2] and studies of body surface isopotential maps[26] have confirmed that this region is excited earlier than normal. According to Durrer and associates,[24] the leftward shift of the vectorcardiographic loop which occurs after 30 to 40 milliseconds may be due to the fact that the posterobasal area is by that time wholly depolarized thus leaving the excitatory forces directed to the lateral and anterior parts of the left ventricle unopposed. Histologic data concerning the peripheral portions of the left bundle are scanty and highly controversial.[24] If the superior division is underdeveloped as sometimes reported[25] the further delay of excitation in the anterior part of the left ventricle will increase the left axis shift as was probably the case in one of Durrer's patients where a delay of the epicardial excitation of the anterior left ventricular wall was recorded.

The anatomical findings of Feldt and colleagues are limited to 8 hearts in which the location and size of the defect are not stated It is possible that the deformities

of the conduction system that they observed are not present in all the cases of ventricular septal defect with an atrioventricular canal type of electrocardiogram. Conceivably interruption of the superior left division alone might be responsible for the peculiar spread of excitation in the left ventricle[illegible] in large septal defects, multiple muscular septal defects, and ventricular septal defects with aortic regurgitation.

The right bundle branch block pattern also deserves some comments The diagnosis of right bundle branch block is difficult to assert in the presence of right ventricular hypertrophy It is likely that *the criteria used in this paper for the diagnosis* of right bundle branch block allow inclusion of patients with pure right ventricular hypertrophy and prolonged QRS duration due to increased muscle mass. Nevertheless, a QRS duration of 0 12 second or more is rare in congenital heart diseases with right ventricular hypertrophy[37] and some authors think that this feature associated with electrocardiographic findings otherwise typical of right ventricular hypertrophy is usually indicative of either an accompanying right bundle branch block or of a diffuse intraventricular block.[38]

The conduction abnormalities disclosed after surgery in moderate-sized ventricular *septal defect of the usual type are easier* to understand

The anatomy of the bundles has been well documented in more than 60 cases of ventricular septal defect and tetralogy of Fallot.[illegible] In the infracristal ventricular septal defect the atrioventricular node is normally situated or slightly posterior to its normal position The bundle of His enters the remnant of the membranous septum which usually forms the posterior rim of the defect. In this situation the conduction system is in close relation to the posterior *margin of the orifice (Fig 3)* The bifurcation of the bundle is not always clearly visualized The fibers of the left branch are given off over a wide area along the posterior and posteroinferior aspect of the defect. The first fibers to leave the common bundle are designated for the posterior radiation of the left bundle branch.[illegible] Usually most or all the fibers of the posterior radiation are given off before the left superior branching starts. The left fibers quickly fan out over the left ventricular endocardial surface and are no longer in close relation to the defect once they have left the common bundle. On the other hand the right bundle skirts the lower edge of the orifice, and is permanently in close relation to the ventricular septal defect.

The fairly constant relationship of the bundle to the margin of the orifice seems to explain the frequency of traumatic lesions of the conduction system after surgical repair of the defect. These lesions result from suturing manipulation, or hypoxia,[44] and consist of localized hemorrhages, traumatic disruption by suture, inflammation or infarction.[illegible]

The right bundle with its subendocardial *position in the inferior margin of the defect* is the most highly exposed segment of the conduction pathway This explains the high incidence of right bundle branch block after operation observed in our series as well as in others.[illegible] Right bundle branch block seems to be related to direct trauma to the conduction tissue, since ventriculotomy alone produces minor changes in QRS configuration but not right bundle branch block.[illegible] Supporting this assumption we have not observed any instance of right bundle branch block in the 1[illegible] *children in this series who had a right* ventriculotomy for infundibular resection (but the ventriculotomy was a small one).

It has been previously stated that the bulk of the left bundle fibers are not as intimately related to the defect as those of the right bundle branch but nevertheless, these fibers are also frequently damaged.[illegible] From Fig 3 it is obvious that the fibers of the superior division of the left branch may be injured at surgery at the same time as the right branch In this condition the postoperative electrocardiogram will show right bundle branch block and left axis deviation of the mid vector

This association was not uncommon after surgery in our series although we could not find in the literature any report on its incidence after correction of a ventricular septal defect. In these, as in most patients who had the atrioventricular canal type of electrocardiogram prior to

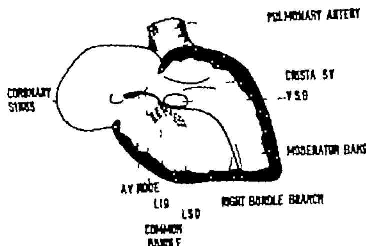


Fig. 3. Ventricular conduction system in infracristal ventricular septal defect. *Crista SV*, crista supraventricularis. *VSD*, ventricular septal defect. *LSD*, superior division of the left bundle. *LID*, inferior division of the left bundle.

surgery, atrioventricular excitation seems to depend primarily on the conduction of the inferior division of the left branch. Complete atrioventricular dissociation represents a permanent threat, especially after surgery. Indeed, this complication occurred in the postoperative period of 15 out of the 45 patients (33 per cent) who showed the atrioventricular canal type of electrocardiogram either before or after surgery.

It has to be noted that complete heart block may also result from damage to the common bundle.[a, a] The incidence of complete heart block was high before 1960 (from 6 to 16 per cent)[44] but this complication has nearly disappeared in the last few years with improvement in surgical technique. Our incidence of 1.05 per cent is in accordance with the other series (0.9 per cent[44] to 1.1 per cent[46]).

Conclusions and summary

The preoperative and postoperative electrocardiograms of 282 patients with ventricular septal defect were studied. There were 140 patients with isolated ventricular septal defect, 136 patients with the tetralogy of Fallot, and 6 patients with the complete form of an atrioventricular canal defect.

Left deviation of the mean QRS axis was present preoperatively in 6 patients. In addition to the 6 patients with an atrioventricular canal, 8 patients with an isolated ventricular septal defect and 7 patients with the tetralogy of Fallot showed an atrioventricular canal type of electrocardiogram prior to operation.

These conduction disturbances seemed to be related to abnormalities of the conduction system producing premature excitation of the posterobasal area of the left ventricle or left superior intraventricular block or both.

Left deviation of the mean QRS axis occurred at operation in only one patient who developed myocardial infarction due to a difficult perfusion.

Right bundle branch block and left axis deviation of the mid vector was a postoperative feature in 24 patients. In all but two cases, the defect was an uncomplicated infracristal moderate-sized ventricular septal defect.

This electrocardiographic pattern, appearing after operation, is thought to be related to direct trauma to the fibers of the right branch and to those designated to be the left superior division of the left branch.

Right bundle branch block with left superior intraventricular block represents a dangerous association. In this condition the auriculoventricular excitation depends primarily on the conduction in the fibers of the inferior division of the left branch.

Any lesion to the latter division such as

invasion by reactive fibrous tissue or surgical trauma would produce complete heart block. This complication was noted in the postoperative period in 33 per cent of our patients who showed an atrioventricular canal type of electrocardiogram either before or after surgery

Complete heart block resulting from the same mechanism might also possibly explain the sudden deaths sometimes observed after surgery in ventricular septal defects.

Although the prognostic implications of the association of right bundle branch block and left axis deviation of the mid vector are not known with precision patients showing that electrocardiographic pattern should be considered a priori as having a poorer prognosis.

We would like to thank Professor J F Goodwin for this research opportunity and for his most helpful direction in the preparation of this paper We are also grateful to Dr C M Oakley for her constructive criticism. We finally acknowledge the help of the Medical Illustration and Photographic Departments and of Mrs. B Vervier for secretarial assistance.

REFERENCES

1 Toscano-Barboza, E., Brandeburg R. O and Burchell H B. Electrocardiographic studies of cases with intracardiac malformations of the atrioventricular canal, Proc. M yo Clin. 31:513 1956.

2. Beregovich, J Bleifer S Donoso, E. and Grishman, A The vectorcardiogram and electrocardiogram in persistent common atrioventricular canal, Circulation 21:63 1960.

3 Burchell H B D Shane, J W and Brandeburg, R. O The electrocardiogram of patients with atrioventricular cushion defects, Am J Cardiol. 6:575 1960.

4 Pileggi, F Boccalandro, I Ebaid, M Melletta, C. A Tranchesi, J Macruz, P and Decourt, L. The vectorcardiogram in interatrial septal defects and persistent atrioventricular canal, Am. Heart J 62:417 1961

5. Neufeld, H N Titus, J L D Shane, J W Burchell, H. B and Edwards, J E.: Isolated ventricular septal defects of the persistent common atrioventricular canal type, Circulation 23:685 1961

6. Du Shane, J W Weidman, W H., Brandeburg R. D and Kirklin, J W Differentiation of interatrial communications by clinical methods. Ostium secundum ostium primum, common atrium, total anomalous venous drainage, Circulation 21:363 1960.

7 Lambert, E. C., Kelsch, J W and Vlad P: Differential diagnosis of ventricular septal defect in children common problem Am. J Cardiol. 11:447 1963.

8. Toscano-Barboza, E., and D Shane, J W Ventricular septal defects correlation of the electrocardiographic and hemodynamic findings in 60 proven cases, Am J Cardiol. 3:721, 1959

9 Feldt, R. H. Du Shane, J W and Titus, J.L. The anatomy of the atrioventricular conduction system in ventricular septal defect and tetralogy of Fallot correlation with the electrocardiogram and vectorcardiogram, Circulation 34 774, 1966

10. Neufeld, H N D Shane, J W Wood, E H. Kirklin, J W and Edwards, J E.. Origin of both great vessels from the right ventricle Circulation 23:399 1961

11 Saab, N G Burchell, H B Du Shane, J W, and Titus, J L. Muscular ventricular septal defects, Am J Cardiol. 18 713 1966.

12. Ellis, F H., J Kirklin, J W Swan, H. J C, Du Shane, J W and Edwards, J E. Diagnosis and surgical treatment of common atrium (cor triloculare biventriculare) Surgery 45:160 1959

13 Heggvest, A. H Congenital aneurysm of the membranous septum, Am. J Cardiol 14:[illegible] 1964

14 Rosenbaum, M B and Lepeschkin, E. Bilateral bundle branch block, Am. Heart J 50:38, 1965.

15 Lenègre, J Contrib tion à l étude des blocs de branch comportant otamment des confrontations électriques et histologiques, Paris 1958 J B. Baillière et Fils.

16 Laham, J À propos d bloc de branche bilatéral, Cardiologia 28:285, 1956.

17 Lepeschkin, E. The electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Progr Cardiovas. Dis. 6:445 1964

18 Puigbo, J J N va-Rhode J R., Garcia Barrios, H Suarez, J R., and Yepez, C. G Clinical and epidemiological study of chronic heart involvement in Chagas disease, Bull WHO 34:650, 1966.

19 Lev M Landowne, M M tchar Jos. C., and Wagner J A. Systematic scleroderma with complete heart block. Report of a case with comprehensive study of the conduction system Am. Heart J 72 13, 1966.

20 Kulbertus, H. E., Coyne, J J and Hallidie Smith, K. A. Electrocardiographic correlation of haemodynamic and anatomical findings in ostium prim m atrial septal defects, Brit. Heart J 30:464 1968.

21 Prato, G H and Bouchard, F Les communications interventriculaires vec axe électrique gauche, Arch. Mal. Coeur 1:50, 1964

22. Brink, A. J and Neill, C. A. The electrocardiogram i congenital heart disease with special reference to left axis deviation, Circulation 12:604, 1955

23. Verduyn-Lunel, A. A. De localisatie van het atrioventriculaire geleidingssysteem bij normale harten en aangeboren openingen in het septum cordis, Dissertation, Leiden, quoted by Durrer et al.,[24] 1964

24 Durrer D Roos, J P and Van Dam, T.: The genesis of the electrocardiogram of patients

ith ostium primum defects (ventral atrial septal defects) AM. HEART J 71:642 1966.
25. Spach, M S., Boineau, J P Long E. C. Gabor J B and Gallie, T M Genesis of the vectorcardiogram (electrocardiogram) in endocardial cushion defects, Proc. L. I Jewish Hosp Symposium on vectorcardiography 1966, North Holland Publishing Co. p. 307
26. Vakili, O Baragan, J and Lenègre, J Les voies de la conduction intracardiaque dans les cardiopathies par anomalie congénitale du septum. Étude anatomique, Arch Mal Coeur 9 1024 1962.
27 Burch G. E., and DePasquale N P Electrocardiography in the diagnosis of congenital heart disease, Philadelphia, 1967 Lea & Febiger Publishers.
28. Massie, E., and Walsh, T J Clinical vectorcardiography and electrocardiography Chicago, 1960, Year Book Medical Publishers, Inc.
29 Watt, T B J Murao, S., and Pruitt, R. D Left axis deviation induced experimentally primate heart, AM. HEART J 70:381 1965
30. Watt, T B., J and Pruitt, R. D Electrocardiographic findings associated with experimental arborization block in dogs, AM. HEART J 69:642, 1965.
31. Pryor R., and Blount, S J The clinical significance of left axis deviation. Left intraventricular blocks, AM. HEART J 72:391 1966
32. Monckeberg J G. Herzmissbildungen ein Atlas angeborener Herzfehler in Querschnitten mit besonderer Berucksichtigung des Atrioventrikularsystems, Jena, 1912, G. Fischer
33. Truex, R. C., and Bishof J K. Conduction system in human heart with interventricular septal defects, J Thoracic Surg 35:421 1958.
34. Uramova, E. Der Verlauf des Reizleitungssystems bei ventrikelseptum Defect, Arch. fur Kreislaufforschung 31:1 1959
35. Lev M The architecture of the conduction system in congenital heart disease, II Tetralogy of Fallot, Arch. Path. 67:572, 1959
36. Lev M The architecture of the conduction system in congenital heart disease, III. Ventricular septal defect, Arch. Path. 70:529 1960.
37 Reemtsma, K., and Copenhaver W M Anatomic studies of the cardiac conduction system in congenital malformation of the heart, Circulation 17:271 1958.
38. Richter M Die Topographie des ventrikelseptum Defects und seine Beziehung zum Reizleitungssystem Thoraxchirurgie 4:56, 1960.
39 Lev M The normal anatomy of the conduction system in man and its pathology in atrioventricular block, Ann New York Acad. Sc. 111:817 1964.
40. Thung, N Dammann J F Diaz Perez, R., Thompson W J Sanmarco, M and Mehegan, C. Hypoxia as a cause of hemorrhage int the cardiac conduction system, arrhythmia and sudden death, J Thoracic & Cardiovas. S. 44:687 1962.
41 Lev M Fell, E. H., Arcilla, R. and Weinberg, M. H Surgical injury to the conduction system in ventricular septal defect, Am. J Cardiol 14:464, 1964
42 Titus, J L., Daugherty G. W Kirklin, J W and Edwards, J E. Lesions of the atrioventricular conduction system after repair of ventricular septal defects, Circulation 27:82, 1963
43 Bristow J D Kassebaum, D G. Starr, A. and Griswald, H. E Observations on the occurrence of right bundle branch block following open repair of ventricular septal defects, Circulation 22:896, 1960
44. Lauer R. M., Ongley P A., D Shane, J W and Kirklin, J W Heart block after repair of ventricular septal defect in children Circulation 22:526, 1960.
45 M Goon, D C., Ongley P A. and Kirklin, J W Surgical induced heart block, Ann. New York Acad. Sc. 3:830, 1964.
46 Gerbode, F Kerth W J Keen, G. K., Ogata, T Popper R. W and Osborn J J Surgical heart block, West S. A. T 70:205 1962.

Indications for anticoagulant therapy

Alan F Lyon M.D
Arthur C DeGraff M.D **
Brooklyn and New York N Y

In the period of almost thirty years in which drugs capable of retarding clotting of the blood in vivo have been available, their use has been recommended for a wide variety of clinical conditions. Since most of these conditions have a variable clinical course and since the anti coagulants do not give complete protection against clotting or its consequences in the conditions in which they are used clinical assessment of their effectiveness has been difficult, and there is still considerable uncertainty as to their clinical role.

Both in regard to clinical indications for anticoagulant therapy and the type and duration of anticoagulant therapy there is some information from biostatistically well-controlled prospective trials which can be given solid credence, and other information, based on uncontrolled clinical observations, which must be accepted with caution.

We shall summarize the type of conditions in which anticoagulant therapy has been proposed and the type of evidence supporting each indication.

Venous thromboembolism

One of the clinical situations in which the value of anticoagulant therapy is best established is pulmonary embolism secondary to venous thrombosis. In a well controlled study reported in 1960 Barrett and Jordan[1] showed that patients begun on anticoagulant therapy after the discovery of evidence of pulmonary embolism had a strikingly lower mortality rate than those not so treated This study not only established the value of anticoagulants in this situation but also since the favorable effect must have been due to a reduction of venous thrombosis as the source of further emboli the study gave support to the many large but less well-controlled studies reported a decade and more before that concluded that anticoagulants were indicated in the presence of deep vein thrombosis. The conclusion of these older studies that anticoagulants, in addition to reducing the morbidity and mortality rates from pulmonary embolism also reduce the duration and degree of involvement at the site of the thrombosis, is less well established Further there is no definite evidence as to the optimal duration of anticoagulant therapy after a pulmonary embolus or venous thrombosis, and we have only a clinical impression to support the notion that a patient with chronic venous insufficiency and recurrent pulmonary emboli is improved by chronic use of anticoagulants rather than treatment of specific episodes of thrombosis and during periods of high

*Clinical Associate Professor of Medicine, State University of New York Downstate Medical Center Brooklyn, N Y and Chief Cardiology Section, Brookdale Hospital Center Brooklyn, N Y
**Professor of Therapeutics, New York University School of Medicine, New York, N. Y and Attending Physician, Bellevue Hospital, New York, N Y

 January 1969 Vol 77 No. 1 pp [illegible]

risk such as enforced bed rest and general anesthesia. The role of anticoagulants in superficial thrombophlebitis is not at all clear

Venous thrombosis and pulmonary embolism can complicate the course of chronic congestive failure often with little clinical evidence of their occurrence. Anticoagulants have been used in this situation with what was considered to be excellent effect. It is of note that the largest and most impressive series demonstrating beneficial effect of anticoagulants in this situation was published prior to 1958 and the introduction of effective oral diuretics. It is likely that the chronically edematous patients described are seen less frequently today When chronic congestive failure does occur the logic and evidence for the use of anticoagulants is still good especially when edema is marked and strict rest is prescribed

Closely related is the problem of venous thromboses and pulmonary embolism complicating surgery Clinical studies have repeatedly suggested that anticoagulants reduced these complications in the postoperative patient, or indeed in the patient with prolonged bed rest for any reason. Particularly well-controlled studies have demonstrated a favorable effect of anticoagulants following repair of hip fracture in the elderly and in some clinics this has become standard practice Others have indicated that they can reduce thromboembolic complications in such patients by careful wrapping of the legs and early ambulation. There is no reason to doubt that the combination of leg wrapping early ambulation, and anticoagulation would offer the best protection to high-risk patients.

It is felt by many that wide-scale anticoagulant therapy for postoperative or immobilized patients is impractical nonetheless, the published experience indicates that such treatment should be used at least in high-risk patients, those who are obese those who have venous insufficiency those with congestive heart failure, or those in whom early ambulation will not be possible.

Another site where thrombosis has been treated with anticoagulants is that of the central vein of the retina. The results of large and long term (but not controlled) studies suggest that early anticoagulation may favor retention of visual acuity and reduce the incidence of hemorrhagic glaucoma in central retinal vein thrombosis, but has no demonstrable effect in the less hazardous branch vein thrombosis.

Arterial occlusive disease

The theoretical value of anticoagulant therapy in arterial occlusive disease is less clear than in venous thromboembolism since extensive intimal disease is more likely to be present and to provide a strong local stimulus to clot formation despite anticoagulants. The clinical results in arterial disease have as one would expect, been variable and often unimpressive.

1 Cerebral vascular disease. There is now nearly general agreement, despite some early studies that suggested limited effectiveness, that anticoagulants have no place, either acutely or chronically in the patient with a completed stroke. The data regarding the progressing stroke in which signs develop slowly over hours to days are less clear Rather small series have led some to suggest that immediate anticoagulant therapy is helpful other results have been equivocal, since patients in this category are few in number

The most impressive benefits of anticoagulants in cerebrovascular disease have been in recurrent ischemic attacks—the recurrent reversible, neurologic dysfunction that often heralds cerebral infarction Here not only extensive clinical observation but several controlled studies suggest a distinct reduction of the number of ischemic episodes and of subsequent infarctions. There is general if not complete agreement that in those patients not suitable for corrective vascular surgery anticoagulants are the best available treatment for recurrent ischemic episodes.

2 Acute occlusive arterial disease of the lower extremities There is general agreement among vascular surgeons, though little in the way of controlled data, that anticoagulants play a valuable protective role in preventing rethrombosis following removal of an embolus or thrombus from the acutely occluded artery Indeed anti

coagulants are considered a valuable adjunct to many forms of vascular surgery. The role of anticoagulants in acute arterial occlusion managed *without surgery is not* at all established.

3. Chronic occlusive arterial disease of the lower extremities. There is no good evidence that anticoagulants affect the course of peripheral arteriosclerosis; several controlled studies that included arteriography suggested some differences in patency of the large vessels, but no effect that could be detected clinically.

Peripheral arterial embolization

There are impressive clinical studies, which, though not rigidly controlled, show such marked reduction in the number of systemic emboli occurring in patients with mitral valve disease when treated with anticoagulants, that these studies can be accepted as evidence of the efficacy of long-term anticoagulant therapy in this situation. Similarly, the experience of clinics following large numbers of patients with valvular protheses has shown a much *higher incidence of emboli in patients* followed without anticoagulants than in patients treated with them so that this has become standard therapy, again in the absence of a rigidly controlled study. The evidence for the use of anticoagulants before and during the conversion of patients with atrial fibrillation to sinus rhythm by electrical or pharmacological means is much less clear. This is to be expected since the incidence of embolization in this situation is quite low. Although the relatively small series available does not permit a final answer, it is the authors' practice to use anticoagulants for a week prior to attempting conversion of chronic atrial fibrillation in patients with mitral valve disease even if they have not previously demonstrated embolism.

Finally, considerable evidence, largely retrospective in type, has been obtained that suggests that anticoagulant therapy begun several weeks before and continued right through the operative period could reduce the incidence of systemic embolization in patients, especially those in Class IV, undergoing closed mitral valvulotomy. With the decline of this procedure in recent years in favor of open valvulotomy this type of prophylaxis is no longer necessary.

Coronary artery disease

The indications for anticoagulant therapy in coronary disease have provoked the most debate and the greatest differences in opinion. The clinical studies are most difficult to interpret. It is now over thirty years since the introduction of anticoagulants for this condition, yet after clinical reports numbering in the hundreds with dozens of well-controlled studies, no final statement can be made about the use of anticoagulants in any aspect of coronary artery disease.

1. Short-term use in acute myocardial infarction. The innumerable small and/or uncontrolled studies attesting to the value of anticoagulants *in acute myocardial* infarction have little actual value. The report of the Cooperative Study of the American Heart Association, a large, fairly well-controlled prospective study first reported in 1948, that anticoagulants have *a definite protective effect, still remains* the strongest evidence in favor of the use of anticoagulants. The large and fairly well-controlled study of Hilden and associates[9] from four Danish hospitals reported in 1960, which reported no difference in *mortality* rates between the treated and control groups, remains the strongest negative evidence.

Although both these reports represent important pioneering biostatistically controlled field trials, they leave something to be desired from a statistician's point of view. The difference between them, moreover, is not as great as would appear at first view; both suggest a distinct reduction in thromboembolic complications. On the basis of present data the interpretations that anticoagulants should be used in all patients, or no patients, or only in those patients with a high risk of thromboembolism, are all defensible. Because of this uncertainty, the Veterans Administration began another cooperative study of this problem designed to avoid the weakness of the previous projects, and perhaps, give a final answer. The results of this study are not yet available.

2 *Long-term therapy after myocardial infarction* Much of the initial enthusiasm for long term anticoagulant therapy following myocardial infarction has waned Nonetheless a number of large, well controlled studies including that of the Working Party of the British Medical Research Council, that of Berkelund and that of the Veterans Administration suggest that there is a small but statistically significant reduction in the mortality rate in men under 55 treated with anticoagulants at least for the first year or two. Several of the studies suggest that there is an even greater reduction in identifiable reinfarctions. These results are theoretically as well as practically important, since this is the group in which the difference in mortality rates is least likely to be due to venous thromboembolism and it is thus likely that the effect produced is on the arterial lesion itself It has been inferred from these reports that there is no point in continuing anticoagulants beyond two years. It would be better stated that there is no evidence establishing the value of continuing treatment beyond this point, since the lack of statistical significance beyond two years may well be due to reduced sample size and excessive number of patients dropping out from protocol. It is hoped that the results of the international cooperative study pooling the data from several of these studies as much as possible, will clarify this question.

3 *Angina pectoris* There is remarkably little evidence from controlled studies as to the effectiveness of anticoagulant therapy in angina pectoris a moderate-sized controlled study reported from Norway a decade ago suggested some benefit when used within the first two years after the onset of angina. Little supporting evidence has developed since and the lack of general usage of anticoagulants in this situation suggests that most clinicians have not been impressed with the effectiveness of anticoagulants in this syndrome, current emphasis being more oriented to the use of surgery and beta adrenergic blocking drugs.

4 *Impending myocardial infarction* The lack of evidence for the effectiveness of anticoagulants in impending myocardial infarction syndrome is not surprising because the difficulty in obtaining agreement on clinical criteria for this diagnosis has made it impossible to mount the large scale controlled cooperative study that would be required to establish clearly significant results. Thus, all that is available are uncontrolled clinical studies, some of which are quite favorable and some not, and upon which a conclusion cannot be based

Further evidence is unlikely to develop in this area the authors have chosen, on a priori grounds, primarily the parallel with progressing strokes where anticoagulants would seem to have some value, to use anticoagulant therapy in these patients.

It is disconcerting to realize that after such prolonged and extensive clinical trial, the scientific justification for the use of anticoagulants is not available in many clinical situations in which they are used it is even more disconcerting to recognize that in some of these areas, because of the difficulty in assessing the clinical data, a final conclusion may never be available It is perhaps most disturbing that in many situations in which anticoagulants are of proved value they are not being extensively used.

Summary

The value of anticoagulant therapy is solidly established in the presence of deep-vein thrombosis and pulmonary embolism in the presence of recurrent cerebral ischemic episodes when reparative vascular surgery is not possible and in postoperative and bedridden patients at least those with a high risk of pulmonary embolism.

There is strongly suggestive evidence for the use of anticoagulants in the presence of recurrent systemic emboli due to mitral valve disease, in patients with valvular prostheses, and in patients immediately following reparative vascular surgery There is suggestive evidence favoring the use of anticoagulants in progressive strokes in men under 55 for two years after myocardial infarction, and in central retinal vein thrombosis.

In all other areas in which they are used

the evidence for the use of anticoagulant drugs remains quite uncertain

REFERENCES

1. Merskey, C., and Drapkin, A.: Anticoagulant therapy, Blood 25:567, 1965.
2. Sevitt, S., and Gallagher, N. G.: Prevention of venous thrombosis and pulmonary embolism in injured patients, Lancet 2:981, 1959.
3. Barrett, D., and Jordan, S. C.: Anticoagulant drugs in the treatment of pulmonary embolism, Lancet 1:1309, 1960.
4. Cooperative study (Veterans Administration): Long term anticoagulant therapy after myocardial infarction, J.A.M.A. 193:929, 1965.
5. Borchgrevink, C. F.: Long-term anticoagulant therapy in angina pectoris, Lancet 1:449, 196_.
6. Hilden, T., Iversen, K., Raaschou, F., and Schwartz, M.: Anticoagulants in acute myocardial infarction, Lancet 2:326, 1961.
7. Cooperative Study (Veterans Administration): An evaluation of anticoagulant therapy in the treatment of cerebrovascular disease, Neurology 11:132 (suppl.), 1961.

Annotations

Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment

In the August, 1967 issue of this JOURNAL, an interesting communication with the above title appeared. By means of combined treatment with propranolol and quinidine the author had obtained a remarkably high conversion rate of chronic atrial fibrillation in that sinus rhythm was achieved in 15 of 18 trials. This communication encouraged us to undertake an identical trial the results of which are presented below.

The study was carried out in 21 consecutive patients with unselected chronic atrial fibrillation. In none of them frank heart failure or known hypersensitivity to quinidine were present. Further informations of the material are given in Table I.

Of the 12 patients with rheumatic heart disease 8 had previously undergone mitral commissurotomy and 2 had been operated upon with transplantation of an aortic valve prosthesis. Three patients suffered from marked mitral insufficiency.

One patient had been operated upon with closure of an atrial septal defect 1 month prior to the trial. Two patients had the condition termed "lone fibrillation."

The trial for conversion was conducted as suggested by Stern.

Of the 21 trials conducted, one had a fatal outcome. This patient (No. 12) suffered from chronic myocarditis with atrial fibrillation. The latter had been successfully treated by means of electroconversion 2 months earlier but had recurred. Digitalis medication was stopped for 3 days and treatment with propranolol started. He received 10 mg. at 8 o'clock and again at 12 o'clock. Three hours later the patient complained of nausea and tiredness, and a pulse rate of 36 per minute and a systolic blood pressure of less than 80 mm. Hg were recorded. Immediate treatment with isoprenaline and metaraminol was started. However, the ventricular rate was observed on the oscilloscope to decrease rapidly until asystole. All measures for resuscitation were unsuccessful. Autopsy revealed extensive myocardial fibrosis in a heart weighing 450 Gm. The lungs contained no excess fluid but were the site of marked fibrosis.

In another patient (No. 2), conversion to sinus rhythm occurred on the second day of the combined treatment. However, the rhythm was extremely slow with only 30 beats per minute and accompanied by coupled ventricular extrasystoles. The treatment was consequently discontinued immediately. The following morning the atrial fibrillation had recurred with a ventricular rate of 100 per minute. Later in the same day the patient suddenly was struck by a cerebral embolus producing coma and hemiparesis. He did not recover and died 1 week later.

The treatment also had to be stopped in a third patient (No. 13) because of severe nausea and dizziness.

Among the remaining 18 patients, conversion to sinus rhythm occurred in 4 patients, one of which (No. 16) reverted on the initial treatment with propranolol alone.

Thus, a total of 14 patients did not respond to the combined treatment with conversion to sinus rhythm. All these patients were afterward subjected to electroconversion whereby sinus rhythm was obtained in 12 patients.

Some undesirable effects of the treatment were observed. In 9 patients, severe bradycardia with ventricular rates down to 30 per minute occurred. Significant fall of the blood pressure was noted in 12 patients in addition to the patient who died and whose hypotension was severe. Troublesome nausea and dizziness were observed in 7 patients. In no case was overt heart failure precipitated by the employed treatment.

The results of the present study were disappointing and are thus in contrast to the favorable results obtained by Stern. Not only was the rate of conversion to sinus rhythm low but the treatment proved to be dangerous.

One patient obviously died as a direct result of the treatment. The rapid development of bradycardia, hypotension, and ultimate asystole are all typical effects of beta-adrenergic receptor blockade.[2,3] In a recent series of 15 patients treated with propranolol, Wennevold and Sandoe[4] observed 3 deaths in asystole. At least 2 of these deaths could be ascribed to the use of propranolol. In the detailed analysis by Stephen, of 2,000 patients treated with the same agent 26 deaths were noted. Among these patients propranolol was definitely implicated in 3 and possibly so in 11. Severe hypotension with and without clinical signs of shock were frequently encountered. Similar but less extensive reactions were also registered in the present study and could have been disastrous by using greater

Table I. Details of the combined therapy in 21 patients

Patients	Sex	Age (yr.)	Etiology	Duration of A F	Previous attempts at conversion	Propranolol pretreatment: Dose daily (mg.)	Propranolol pretreatment: No. of days	Propranolol and quinidine: Dose daily (Gm.) of quinidine	Propranolol and quinidine: No. of days	Success of conversion	Follow-up period (mo.)
1	F	68	RHD	5 mo.	No	40	2	1.2	5	No	
2	M	67	ASCVD	2 mo.	No	40	3	0.8	2	Yes	
3	F	71	HHD	5 yr.	N	40	3	0.8	4	Yes	
4	M	49	RHD	1 yr.	N	30	3	1.2	5	No	
5	M	45	ASD	9 yr.	No	30	2	0.6	4	No	
6.	F	44	RHD	6 mo.	N	30	2	1.2	7	No	
7	F	57	RHD	7 yr.	N	40	3	0.8	3	Yes	2
8	F	52	RHD	1 yr.	1	40	3	1.2	6	No	
9	M	51	MC	3 yr.	3	40	3	1.2	6	No	
10	M	57	MC	1 yr.	1	40	4	1.2	6	No	
11	M	46	RHD	8 yr.	4	60	3	1.2	6	No	
12.	M	33	MC	3 mo.	1	20	1			No	
13	M	53	RHD	1 yr.	N	40	3			No	
14	M	22	LF	1 yr.	No	60	3	1.2	6	No	
15	F	53	RHD	6 yr.	2	40	2	1.2	7	N	
16.	M	50	LF	1 yr.	N	40	2			Yes	2
17	F	47	RHD	1 yr.	1	40	2	0.8	5	Yes	2
18.	M	47	SMAS	3 yr.	3	60	3	1.2	7	No	
19	F	49	RHD	8 yr.	1	30	3	1.0	5	No	
20	M	56	RHD	2 yr.	No	40	3	1.2	7	No	
21	F	55	RHD	5 yr.	No	40	3	1.2	6	N	

RHD, Rheumatic heart disease; ASCVD, arteriosclerotic cardiovascular disease; LF, lone fibrillation; MC, chronic myocarditis; and SMAS, subvalvular muscular aortic stenosis.

doses or by prolonging the trial. The tolerance to beta-adrenergic blocking drugs is namely decreasing with time, a fact which has not been thoroughly stressed.

Quinidine and propranolol have several effects in common. Both have local anesthetic properties and both increase the electrical threshold for stimuli in the heart, increase the fibrillatory threshold, and decrease the conduction velocity. In addition, since the antiarrhythmic action of propranolol is independent of its beta-adrenergic blocking activity, the drug has been regarded to be more or less similar to quinidine.[1,8] From these points of view a combination of the 2 drugs would probably offer advantages in the treatment of arrhythmias.

Unfortunately, clinical experience does not support this consideration. In contrast to quinidine, propranolol has proved to be ineffective in restoring as well as in maintaining sinus rhythm in chronic atrial fibrillation.[1,4,7] The only specific indication for treatment with propranolol is still digitalis-induced ventricular tachycardia.

One more difference exists between quinidine and propranolol in that the former facilitates and the latter inhibits the atrioventricular impulse conduction. In the present trial, propranolol heavily overruled quinidine in this respect as demonstrated by the occurrence of severe bradycardia in several patients. Virtual blockade of the sinoatrial or atrioventricular conduction was not observed, although this is well known from other series.[4,7]

Overt heart failure was not met with as a direct result of the treatment in this study. This was to be expected for the reason that both quinidine and propranolol possess marked depressant actions upon the myocardium.[3,4] More so because several of our patients had compensated heart failure with pulmonary congestion and because the sympathetic drive is so beneficial for the failing heart. The explanation may be that the patients were only allowed to undertake minimal physical effort during the trial and were closely supervised.

Hypotension has not consistently but rather frequently been observed during treatment with propranolol as was the case in the present study. The cause of this blood pressure fall may sometimes be decreased systemic arterial resistance,[10] but in most instances the cause is a decrease in cardiac output. It has been conclusively demonstrated in acute experiments that blood pressure and cardiac output decrease to the same extent. Consequently control of blood pressure remains essential in assessing the cardiac effects of beta-adrenergic blockade.

In the large material collected by Stephen, notable side effects by treatment with propranolol were recorded in less than 2 per cent. According to the experience of this report this figure is low as one third of the patients complained of troublesome nausea, tiredness, lightheadedness, and mild dyspepsia. However the treatment had to be discontinued for these reasons in only one patient.

In conclusion, the present report does not provide evidence that combined treatment with quinidine and propranolol is effective in converting chronic atrial fibrillation to sinus rhythm. More so, this report provides evidence that the treatment may be dangerous.

It is also to be observed that in the majority of the patients, who did not obtain sinus rhythm on the combined treatment, successful restoration of sinus rhythm was easily achieved by means of electroconversion.

L. Hillestad, M.D
O. Størstein, M.D
Department of Medicine B
University Hospital
Rikshospitalet Oslo Norway

REFERENCES

1. Stern, S. Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment, AM. HEART J 74:170, 1967
2. Epstein, S. E., and Braunwald, E. Beta-adrenergic blocking drugs, New England J Med. 275:1175, 1965.
3. Rouse, W. Effects of propranolol and ouabain on conducting system of heart in dogs, Am. J Cardiol. 18:406, 1966.
4. Wennevold, A., and Sandée, E.: Propranolol (Inderal) ved behandling av arytmier, Ugeskr Laeger 128:789, 1966.
5. Stephen, S. A. Unwanted effects of propranolol, Am. J Cardiol. 18:463, 1966.
6. Gianelly, R., Griffin, J. R., and Harrison, D. C. Propranolol in the treatment and prevention of cardiac arrhythmias, Ann. Int. Med. 66:667, 1967
7. Lurie, M. H., Adelson, E. I., and Miller, A. J. Acute and chronic effects of an adrenergic beta-receptor blocking agent (propranolol) in the treatment of cardiac arrhythmias, Circulation 31:767, 1966.
8. Aroesty, J. M., and Cohen, J. The effects of a beta-adrenergic blocking agent, pronethalol, on digitalis-induced ventricular arrhythmias, AM. HEART J 71:503, 1966.
9. Welch, G. A., Braunwald, E., Case, R. B., and Sarnoff, S. J. The effect of mephentermine sulphate on myocardial oxygen consumption, myocardial efficiency and peripheral vascular resistance, Am. J. Med. 24:871, 1958.
10. Schroeder, G., and Werkö, L. Hemodynamic studies and clinical experience with nethalide beta-adrenergic blocking agent, Am. J. Cardiol 15:58, 1965

Blood rheology in pathogenesis of the coronary heart diseases*

The study of coronary heart diseases was concerned mainly with the pathogenetic pathways via the abnormalities of blood pressure, metabolism, dietary regime, formation of atherosclerotic plaques, stress, cholesterol levels, etc., but the role of blood viscosity was rather neglected. In the more recent time the rheology of blood was studied by a great number of investigators, while its possible role in the myocardial infarction and coronary occlusion was indicated during 1962 by Burch and DePasquale[1] and Dintenfass.

In the following years, in a series of papers,[2-9] an idea was promoted that the viscosity of blood represents the key factor in the physiology and pathology of circulation due, mainly to the very complex rheologic characteristics of the whole blood.

Blood was found to be a triple-thixotropic fluid in which each of the subphases shows a different response to the flow (velocity gradient). The viscosity of blood is affected not only by the flow velocity but also by the quantitative aspects of these subphases, i.e. hematocrit, aggregation of the red cells, the internal viscosity of the red cell, and plasma viscosity.

While at near zero flow velocities, the whole blood might exhibit viscosities from 100- to 10 000-fold that of water, at high flow velocities it is only 2- to 10-fold that of water. Perhaps the most remarkable aspect of blood is that it remains fluid even at hematocrits of 95 and 100 per cent. Indeed, at these hematocrits the viscosity of blood can be as low as 20 centipoises, if tested at high flow velocities. In contradistinction to blood, suspensions of rigid particles achieve the consistency of a brick already at concentrations of 65 per cent.[10-13]

Viscosity of blood is influenced both by hematocrit and by the internal viscosity of the red cell, although the latter is of little significance at very low hematocrits (Fig. 1). The internal viscosity of the red cell becomes significant at hematocrits

*Work supported by the National Heart Foundation of Australia.

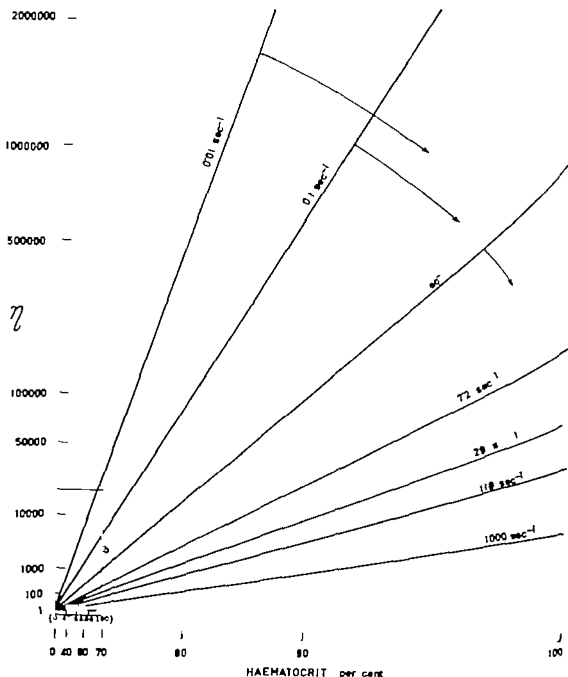


Fig. 1A. Viscosity of blood as function of hematocrit and flow velocity for normal and sickled or crenated red cells. Blood viscosity is plotted, in centipoises, as a function of hematocrit. The small scale (insert a-b) corresponds to the normal blood the large hematocrit scale corresponds to the blood containing crenated red cells or sickle cells. Each curve represents a different velocity gradient (different flow velocity) marked in sec.$^{-1}$ Please note that at hematocrits below 40 per cent the viscosities of normal blood and of blood containing sickle or crenated cells is nearly equal. The arrows (top of the graph) indicate that the blood viscosity at very low shear rates might be less than indicated. Velocity gradient affects blood viscosity by decreasing the internal viscosity of the red cell and by decreasing the degree of aggregation of the red cells. Nonlinear coordinates are used. This graph is intended as an illustration mainly

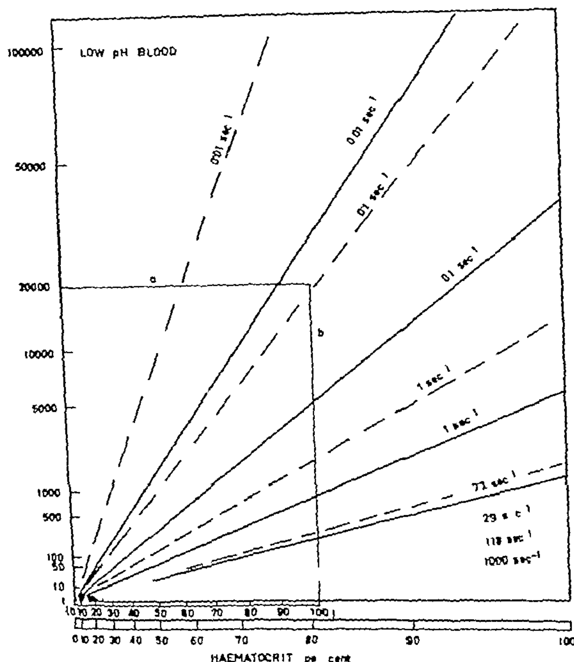


Fig. 1B Viscosity of blood as a function of hematocrit, velocity gradient, and the degree of aggregation of the red cells. Relative viscosity of blood, η, that is, the viscosity of blood divided by the viscosity of plasma, is plotted as function of hematocrit. The upper and shorter hematocrit scale (insert a-b) corresponds to normal blood. The full (lower) hematocrit scale corresponds to the low-pH blood. The full lines show the blood viscosities at the degree of aggregation of red cells corresponding to the mean observed in normal. The broken lines show the blood viscosities at the degree of aggregation of red cells corresponding to the mean observed in patients suffering from the coronary occlusion or arterial thrombosis. Insert a-b of this graph is identical to the a-b insert of Fig. 1A. Nonlinear coordinates are used. This graph is intended as an illustration solely

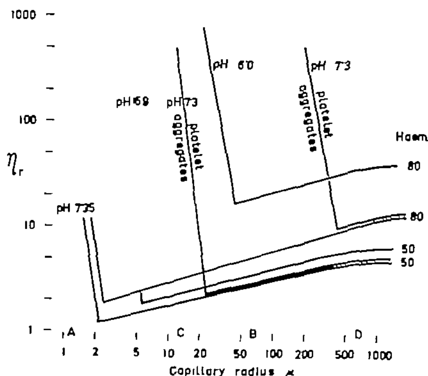


Fig. 2. An inversion phenomenon and the critical capillary radius for blood flow in capillaries and microcapillaries. The relative viscosity of blood, β (= viscosity of blood divided by viscosity of plasma) is plotted against the capillary radius in microns, at flow under constant pressure gradient (approximately 5 cm. H_2O/cm length). A progressive decrease of blood viscosity from right to left is due to the Fahraeus-Lindqvist phenomenon; sudden inversion follows at critical radius depending on blood pH, hematocrit, and the presence or absence of platelet aggregates. The range of critical radii A to B is affected mainly by blood pH and aggregation of the red cells; the range C to D will be primarily affected by the size of platelet aggregates, although smaller platelet aggregates can affect the lower ranges of capillary radii. This graph is intended as an illustration only.

above 40 per cent, and is of paramount importance at hematocrits above 70 per cent. The degree of aggregation of the red cells depends on the shear rate (flow velocity) and on the intrinsic properties of the blood. The size of the red cell aggregate is not permanent or fixed, as aggregation-disaggregation represents a dynamic process. This reversible aggregation of the red cells exists in normal and abnormal blood, although the degree of aggregation may vary greatly.

In the case of blood flow in capillaries, 2 additional phenomena play an important role. First is the Fahraeus-Lindqvist phenomenon in which blood viscosity decreases as the caliber of a capillary decreases, and second is the inverse phenomenon described recently by Dintenfass[14] in which a sudden increase in the viscosity of flowing blood takes place when the capillary bore falls below a certain critical radius. This critical radius (Fig. 2) may be 2 to 10 μ for disaggregated blood and in the absence of platelet aggregates, it may be up to 500 μ in the presence of platelet aggregates, and it can assume any value between 10 and 50 μ depending on blood pH and on the degree of aggregation of the red cells. In effect, one can visualize a spectrum of critical radii depending on the internal viscosity of the red cells, the degree of aggregation of the red cells, and the size of platelet aggregates.

Effect of blood pH, although not as striking as effects of crenation or sickling of the red cells, is physiologically significant.[14,15] In the larger vessels, an increase of the hydrogen ion concentration will lead to a pronounced increase of blood viscosity only at rather high hematocrits. However any elevation of the internal viscosity (or rigidity) of the red cell will have a direct effect on the microcapillary flow at any hematocrit value. Superimposed on the effects of the increased internal viscosity of the red cell comes the aggregation of the red cells which is also increased in hypoxia. As the latter increases the rate of plasma skimming, hemoconcentration in some capillary branches may take place,[16] with consequent large increase in the blood viscosity.

An increase in the viscosity of blood in patients suffering from coronary occlusion and arterial thrombosis was reported in 1962. A four to tenfold viscosity increase, measured at low shear rates,

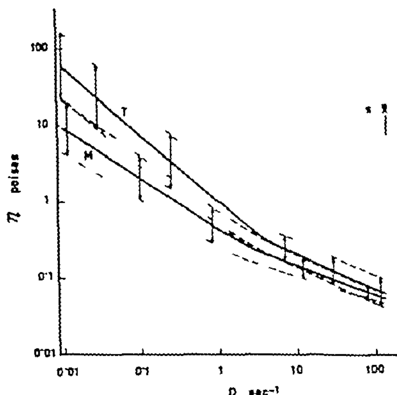


Fig. 3 Blood viscosity in normal controls (M) and in patients (T) suffering from coronary occlusion, myocardial infarction, and arterial thrombosis. Viscosity of blood, in poises, is plotted as a function of the velocity gradient (approximately flow velocity), D in sec^{-1}. Log-log scale is used. The full lines correspond to the arithmetic means, the broken lines to the limits of one standard deviation, s. Please note that blood viscosities of normals and patients diverge increasingly as the velocity gradient decreases. Graph plotted from the data of reference 8.

were ascribed to an increased aggregation of the red cells. This study was repeated subsequently on 100 patients and normal donors[8] and the results are shown in Fig. 3. This and other work[17] led to postulation of the blood high viscosity syndromes.

The syndrome of particular relevance would be the one corresponding to the thrombotic states, and specifically to the coronary heart diseases.

An increase of blood viscosity due to an increased aggregation of the red cells may lead to localized stasis, this in turn increasing the rigidity of the red cells through localized hypoxia. This, again, leads to an increase of blood viscosity, lowered flow rate, a further increase in blood viscosity and, thus, to a further increase of the aggregation of the red cells and of the internal viscosity of the red cell. In the stasis regions, the permeability of capillaries might increase leading to localized hemoconcentration.

An excessive aggregation of the red cells might lead to an increased hemoconcentration through plasma skimming and even more important, to displacement of platelets from the center of the stream toward the near-the-wall (high shear rate) zone, thus, enhancing their adhesive properties and enabling formation of platelet aggregates.[illegible]

While an occlusion of a small capillary can be caused by a single cell (at very low pH), and of larger capillaries by the aggregates or agglutinates of cells, the platelet aggregates can occlude capillaries and small vessels of any size.

The degree of aggregation of red cells can be enhanced by infection, fever, excess of fibrinogen, and presence of macroglobulins, while the aggregation of platelets might be increased by catecholamines or viral infection.[33,34] Hypoxia can enhance not only the rigidity of the red cell but also the degree of platelet aggregation.[33,35]

A capillary stasis, capillary occlusion or capillary thrombosis will lead to localized areas of infarction and tissue necrosis. Capillary occlusion or thrombosis might lead to the pathological changes and necrosis of the heart muscle or of the arterial walls, the latter enhancing possibility of the large-vessel thrombosis. Any damage to the red cell, any deterioration of the red cell membrane, might trigger off a contact activation of plasma clotting; the red cells themselves might contribute clotting factors. The necrotic changes in a vessel wall might also initiate a localized deposition of platelets. A decrease of the lumen facilitates the velocity gradient-enhanced aggregation of platelets.

Virus & toxins
diabetes
genetic factor
abnormal proteins

Increased CRITICAL capillary RADIUS

Occlusion of capillaries

Eddies

Excessive aggregation of the red cell

Increased rigidity of the red cell

HIGH BLOOD VISCOSITY

Predisposition to lodging thrombi or venous thrombosis

Slow down of circulation

Platelets move to the periphery of the blood stream

Reduced oxygen transport; local hypoxia

Adhesiveness and aggregation of platelets increased by flow in the high shear-rate-of zone

Local anoxia local acidosis

Formation of microthrombi & microemboli

Degeneration of arterial walls

Tissue necrosis

Platelet adhesiveness increased by pathology of vessels wall

Stenosis

ARTERIAL THROMBOSIS

MYOCARDIAL INFARCTION

Fig. 4. A diagram representing the hypothesis of the role of rheological factors in pathogenesis of myocardial infarction and arterial thrombosis. The sequence of events is indicated by arrows (thick full lines, full lines, and broken lines, according to the degree of importance). The upper case type and a double frame indicate more important steps.

The more the lumen is decreased, the higher is the velocity gradient in the particular area. For instance, when lumen decreases to ¼ of its original cross section, the blood velocity (at the same flow rate) increases fourfold while the velocity gradient might increase sixteenfold. One can easily envisage that a cumulative aggregation of platelets, speeded up tremendously by the high velocity gradient, will increase the size of the white thrombus till complete closure of the lumen will take place. A way is now open for the formation of zero-velocity red thrombus.

But on the other hand, an excessive aggregation of red cells, especially an excessive aggregation of low pH red cells, might lead to the slowing down of flow in relatively large vessels. Rigid cells will bring up the viscosity of blood, at hematocrits of about 60 per cent, to the consistency of window putty or asphalt.

The smaller the vessel the easier it is to reach the critical radius at which the apparent viscosity of blood will rapidly and greatly increase, and a sudden and dramatic increase in the resistance to flow will take place.

A result of the blood viscosity elevation may be decrease in the cardiac output. This can be directly due to the pathology of the heart itself as affected by the microcapillary occlusions, or by the general increase in the blood viscosity. A slow down of the peripheral circulation might be a direct cause of ischemia and failure of the peripheral tissues (Fig. 4).

While it can be clearly seen that thrombotic states, ischemia, and infarction are related to the blood high viscosity syndrome, a question remains if the elevation of blood viscosity preceded the clinical symptoms. The ultimate answer can be given only by a prospective study.

It is my belief, however, that an elevation of blood viscosity precedes the appearance of clinical symptoms, although a positive feedback—in which the presence of clinical symptoms might aggravate the blood rheology—is quite in order. I have the following grounds for this belief: (1) the viscosity elevation was observed both in acute and in old myocardial infarctions; (2) thrombotic episodes are common to all diseases in which blood viscosity is elevated (i.e., polycythemia, sickle cell disease, some form of cancer, macroglobulinemia); (3) the viscosity of blood in normal human beings does not change with age and remains quite constant between 18 and 80 years of age; the viscosity of blood

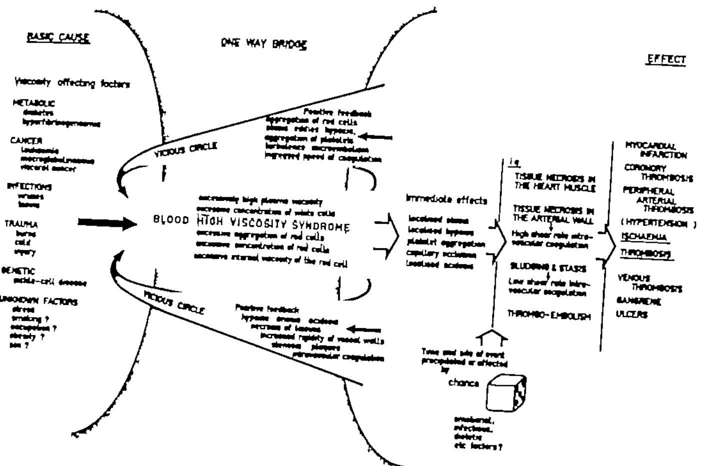


Fig 5 One- ay bridge of the blood high viscosity syndrome This diagram illustrates the role of blood high viscosity in the development of ischemia infarction, nd thrombosis. The basic causes (left) can affect blood viscosity by increasing plasma viscosity ggregation of red cells, internal viscosity of the red cell hemoconcentration, nd concentration of white cells. Immediate effect and vicious circles re indicated. This diagram should be viewed together with Fig 4

in patients appears to increase progressively with age (4) thromboembolic phenomena and myocardial infarctions do take place in patients with impaired coagulation mechanism (hemophilia, von Willebrand disease) and a patient with hemophilia and thrombotic disorder did show elevated viscosity.

It does appear that an elevated blood viscosity is a stage through which all the pathological processes have to pass in order to affect the tissues. It does not matter—in the final count—if this viscosity elevation is due to an increased aggregation of the red cells, increased internal rigidity of the red cells, increased hematocrit increased plasma viscosity or the presence of platelet aggregates. In all cases, such viscosity elevation will lead to the slow down of circulation and localized stasis. The latter may be self perpetuating as the metabolic acidosis following the localized hypoxia will increase the internal viscosity of the red cells and thus, will increase manyfold the viscosity of blood.

The one-way bridge of the high blood viscosity syndrome (Fig 5) may be originated by many causes. These could be divided, perhaps, into 2 groups the basic causal factors and the precipitants. While the former will include polycythemia cancer diabetes genetic or metabolic abnormalities, shock, endotoxins and exotoxins, and unknown causes, the precipitants would include infection, fever diet, emotional stress, trauma physical exertions, etc. Each of these factors can act on one or more *subphases of blood and can influence the rheological* parameters of these subphases. Thus, for instance, infection or fever will increase the degree of aggregation of the red cells emotional stress may lead to release of catecholamines and increased aggregation of platelets physical exercise might lead to dehydration or localized hypoxia increasing the concentration and the internal viscosity of the red cell some forms of cancer and especially leukemia, might elevate greatly the viscosity of blood plasma genetic abnormalities might permit a formation of the sickle cells which are manyfold more rigid than the normal red cells; arterial stenosis might facilitate high-shear-rate formation of platelet aggregates and microemboli, etc.

One or more of the causal factors, or one or more of the precipitants (although both groups can merge) can act at once exerting a synergistic effect on the blood viscosity. Whether the viscosity elevation is due to one or other cause, the fact remains that it is the viscosity elevation, general or localized, which is directly responsible for the slowdown of circulation and especially the microcirculation, and leads to ischemia, necrosis, and infarction because, if the coagulation factors (in the orthodox sense) were the primary cause, the coronary heart diseases would not have been observed in patients with hemophilia and other coagulation defects.

A particular location of infarction or thrombosis can be due to chance that is, it can be due to the localized genetic abnormalities, or due to the sensitization of a particular area by drugs or diet, or due to the hydrodynamics of the flow (i.e., formation of eddies or turbulence), or due to the greatly variable viscosity of blood in the different areas of the body

Myocardial infarction and coronary occlusion might be nonspecific diseases of multitude of etiologies but characterized by a common single pathway of the blood high viscosity syndrome.

The frequency and magnitude of the thrombotic episodes clinically silent, and involving perhaps transient occlusions and infarctions, might be heralded by an increased blood viscosity

Leopold Dintenfass Ph.D M.Sc., F.R.A.C.I.
Hemorheology Unit of Sydney Hospital
and Department of Medicine
University of Sydney
Sydney Australia

REFERENCES

1. Burch, G E., and DePasquale, N P Editorial Hematocrit, blood viscosity and myocardial infarction Am. J Med. 32 161 1962.
2. Dintenfass, L. Thixotropy of blood and proneness to thrombus formation, Circulation Res. 11:233, 1962
3. Dintenfass, L. A study in flow viscosity and clotting of human blood M. J Australia 1:575, 1963
4. Dintenfass, L. Blood rheology in cardiovascular diseases, N ture 199:813 1963.
5. Dintenfass, L. Rheologic approach t thrombosis and atherosclerosis, Angiology 15:333, 1964.
6. Dintenfass, L. Viscosity and clotting of blood in venous thrombosis and coronary occlusions, Circulation Res. 14 1 1964
7. Dintenfass, L. Some rheological factors in pathogenesis of thrombosis, Lancet 2:370, 1965
8. Dintenfass, L. J llan, D G and Miller G Viscosity of blood in normal subjects and in patients suffering from coronary occlusion and arterial thrombosis, Am. Heart J 71:587 1966
9. Dintenfass, L. A preliminary outline of the blood high viscosity syndromes, Arch Int Med. 118:427 1966.
10. Dintenfass, L. Considerations of the internal viscosity of red cell and its effects on the viscosity of whole blood, Angiology 13:333 1962
11. Dintenfass, L. Rheology of the packed red blood cells containing haemoglobins A-A, S-A, and S-S, J Lab & Clin. Med. 64:594 1964
12. Dintenfass, L.: Molecular and rheological considerations of the red cell membrane in view of the internal fluidity of the red cell, Acta Haemat. 32:299 1964
13. Dintenfass, L. Viscosity of the packed red and white cells, Exp. Molec. Path 4:597 1965
14. Dintenfass, L. I version of the Fahraeus-Lindqvist phenomenon in blood flow through capillaries of diminishing radius, Nature 215:1099 1967
15. Dintenfass, L., and Burnard, E. D : Effect of hydrogen ion concentration on in vitro viscosity of packed red cells and blood at high haematocrits, M J Australia 1 1072, 1966
16. Palmer A. A.: A study of blood flow in minute vessels of the pancreatic region of the rat with reference to intermittent corpuscular flow in

individual capillaries, Quart. J. Exper. Physiol. 41:149, 1959.
17. Dintenfass, L., and Rozenberg, M.: Some observations on the viscosity of blood in various diseases. Effect of intravenous heparin, Angiologica 4:116, 1967.
18. Dintenfass, L., and Rozenberg, M.: The influence of the velocity gradient on in vitro blood coagulation and artificial thrombosis, J. Athero-scler. Res. 5:276, 1965.
19. Dintenfass, L.: Effect of velocity gradient on the clotting time of blood and on the consistency of clots formed in vitro, Circulation Res. 18:349, 1966.
20. Ardlie, N. G., Glew, G., and Schwartz, C. J.: Influence of catecholamines on nucleotide-induced platelet aggregation, Nature 212:415, 1966.
21. Mustard, J. F., Glynn, M. F., Nishizawa, E. E., and Packham, M. A.: Platelet-surface interactions: relationship to thrombosis and hemostasis, Fed. Proc. 26:106, 1967.
22. McKay, D. G., and Margaretten, W.: Disseminated intravascular coagulation in virus diseases, Arch. Int. Med. 120:129, 1967.
23. Mahn, J. R., Manger, W. M., Sullivan, S. F., Papper, E. M., and Nahas, G. C.: The effect of acidosis on sympatho-adrenal stimulation, J.A.M.A. 197:121, 1966.
24. Hirsch, H., Haehtgens, P., and Sobbe, A.: Änderungen des Siebungsdrucks nach Ischämie von Gehirn, Extremität und Niere, Pflügers Arch. Physiol. 281:191, 1964.
25. Borchgrevink, C. F.: Myocardial infarction in hemophiliac, Lancet 1:1229, 1959.
26. Stewart, J. W., and Acheson, E. D.: Atherosclerosis in a hemophiliac, Lancet 1:1121, 1957.
27. Green, D., and Rizza, C. R.: Myocardial infarction in a patient with a circulating anticoagulant, Lancet 2:434, 1967.
28. Hoak, J. C., Swanson, L. W., Warner, E. D., and Connor, W. E.: Myocardial infarction associated with severe factor XII deficiency, Lancet 2:884, 1966.
29. Glueck, H. I., and Roehll, W.: Myocardial infarction in a patient with Hageman (Factor XII) defect, Ann. Int. Med. 118:390, 1966.
30. Silver, J., Cronberg, S., and Nilsson, I. M.: Occurrence of arteriosclerosis in von Willebrand disease, Acta med. Scandinav. 180:475, 1966.
31. Dintenfass, L., and Castaldi, P.: A study in viscosity and clotting of blood in haemophiliacs, Thromb. Diath. Haemorrh. 11:267, 1964.

Recommendations for sphygmomanometry
A dissenting opinion

The new report by a subcommittee of the American Heart Association giving recommendations for human blood pressure determinations by sphygmomanometry[1] contains two disappointments. One is the renewed adoption of the "muffled" endpoint as the preferred index for reading diastolic pressure and the other is the failure of the committee to review interim reports concerning cuff design.

The choice of criterion for reading diastolic pressure has been argued since the days when oscillometry was the only method available to assess diastolic pressure. Since the description of Korotkoff sounds, the argument has persisted as to whether the change to a muffled quality of the sounds (Phase IV) or their disappearance (Phase V) represents the "best" indication of diastolic pressure.

The original committee, set up in 1939, recommended the muffled criterion. The subsequent committee report in 1951 changed to the silent endpoint on the basis of the available reports comparing intra-arterial and cuff measurements of diastolic pressure made at both criteria. This recommendation was hailed by Burton as a major setback in medical science.

The renewed adoption of the muffled criterion seems to the present author to have been made on inadequate evidence. The points made in favor of the muffled endpoint are that it is more easily determined and not influenced by the auditory acuity of the observer. It is further added that "the laws of physics associate the point of muffling with diastolic pressure. There is no logical connection between the disappearance of sound and diastolic pressure."

After reviewing the literature on the choice of diastolic endpoint, it must be concluded that neither gives a true measure of diastolic pressure. In the absence of adequate evidence that hemodynamically one or other endpoint is more appropriate, the choice would seem logically to fall to that which is associated with a smaller random error. Holland and Humerfelt[3] showed a smaller variance in silent than in muffled diastolic readings. Armitage and Rose[4] showed a highly significant "between reading" variance in a population of diastolic readings made at the muffled endpoint while the between reading variance was nonsignificant in silent diastolic readings. These carefully designed experiments would seem to show that the silent endpoint is more easily or consistently discerned or possibly that the hemodynamic conditions in the artery are more stable when the sounds disappear. In an

event the findings would favor the silent index for reading diastolic pressure.

The argument given by Burton in an editorial comment supporting the decision for the muffled endpoint is that the high-pitched component of the staccato (Phase III) sounds is generated by a rapid opening of the artery with systole and that muffling occurs when the artery is no longer sufficiently collapsed for this to occur at which point flow becomes continuous. The work of McCutcheon and Rushmer[8] is quoted in favor of this argument but these workers showed in cineangiographs that the artery remained compressed until cuff pressure was below diastolic pressure. They were also unable to show by Doppler flowmeter recordings that flow in the artery became continuous through diastole when the cuff was below the muffling pressure except when reactive hyperemia had been previously induced. These arguments seem inadequate to propose the rejection of the vast store of data and experience that has been accumulated with the silent diastolic endpoint.

While the committee[1] gives a preference for the muffled endpoint, it recommends the recording of both endpoints. Its predecessors[3] had dolefully commented that "the recommendations formulated in 1939 (to record diastolic pressure at both endpoints) has not been followed very generally." It seems likely that this latest recommendation will be followed only when there is a marked difference in muffled and silent diastolic pressures.

The argument concerning the diastolic endpoints will not be resolved until a more complete understanding is gained of the hemodynamic mechanisms involved. Further attention must be paid to the energy content of the arterial wave and to the role played by the circulatory system distal to the cuff.

The recommendations concerning cuff design remain unchanged from the previous committee report despite numerous reports suggesting improvements. Orma and associates were the first in recent times to point out the importance of bladder length as a consideration in cuff design, although this was clearly recognized some 60 years ago. The Finnish group[9] were able to show a correlation between skinfold thickness and blood pressure readings but not with arm circumference when using a standard length bladder (23 cm.). The correlation was reduced with a longer bladder (40 cm.) and random errors were smaller. Simpson and co-workers confirmed a lower intersubject variance within readings made with a long-bladdered cuff (35 cm.) when compared with readings obtained with a standard cuff. King[11] gave experimental evidence tending to disprove the classical hypothesis to explain the effect of cuff width stated again in the current committee report. He was further able to show that when the bladder encircled the arm blood pressure readings were independent of arm circumference and were minimally influenced by cuff width. The falsely high readings obtained when the bladder failed to extend round the arm were not reduced when the bladder was constrained by a stiff cuff backing. Comparisons between the pressures obtained with various cuff designs with intra-arterial measurements showed *that a smaller range of random errors was obtained* with a long bladdered cuff (40 cm.). Karvonen, Simpson and King agree that the bladder provided in the standard cuff is too short.

In view of the finding by King[11] that when the bladder encircles the arm cuff width becomes much less important, the committee was perhaps premature in renewing the earlier recommendations for cuff size for use in children and for the adult thigh before this principle could be tested in these applications.

The 1951 committee began its report with the statement, "It should be clearly recognized that arterial pressures cannot be measured with precision by means of sphygmomanometers." (It is worthy of note that a less forceful statement of this principle has now been submerged in the general text of the new report.) If it is indeed recognized that the cuff and manometer give only an approximate measure of intra-arterial pressure then the assessment of the "goodness" of the method depends on the extent of random errors involved. Since random error can be reduced by the use of the silent diastolic endpoint and a longer bladder in the cuff, then general adoption of these factors would improve the quality of routine sphygmomanometry.

Geoffrey E. King, M.B., B.S.
Assistant Professor of Medicine
Medical College of Georgia
Augusta, Ga.

REFERENCES

1. Subcommittee of the American Heart Association: Recommendations for human blood pressure determination by sphygmomanometers, Circulation 35:988, 1967.
2. Joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland: Standardization of blood pressure readings, J.A.M.A. 113:294, 1939.
3. Committee to revise standardization of high blood pressure readings: Recommendations for human blood pressure determinations by sphygmomanometers, Circulation 4:503, 1951.
4. Burton, A. C.: Peripheral circulation, Ann. Rev. Physiol. 15:213, 1953.
5. Holland, W. W., and Humerfelt, S.: Measurement of blood pressure: comparison of intra-arterial and cuff values, Brit. M. J. 2:1241, 1964.
6. Armitage, P., and Rose, G. A.: The variability of measurements of casual blood pressure. I. A laboratory study, Clin. Sc. 30:325, 1966.
7. Burton, A. C.: The criterion for diastolic pressure—revolution and counterrevolution, Circulation 36:805, 1967.
8. McCutcheon, E. P., and Rushmer, R. F.: Korotkoff sounds, an experimental critique, Circulation Res. 20:149, 1967.
9. Orma, E., Punsar, S., and Karvonen, M. J.: Cuff hypertension, Duodecim 76:160, 1960.

10. Karvonen, M. J., Telivuo, L. J., and Jarvinen, E. J.: Sphygmomanometer cuff size and the accuracy of indirect measurement of blood pressure, Am. J. Cardiol. 13:688, 1964.
11. Simpson, J. A., Jamieson, G., Dickhaus, D. W., and Grover, R. F.: Effect of size of cuff bladder on accuracy of measurement of indirect blood pressure, Am. Heart J. 70:208, 1965.
12. King, G. E.: Errors in clinical measurement of blood pressure in obesity, Clin. Sc. 32:223, 1966.

On prescribing the climate

Bed rest, diet, drugs, surgery, physical rehabilitation, and psychotherapy either alone or in combination are among the procedures regularly prescribed by physicians in the management of diseases. The influence of climate upon man and his health, although known since ancient time, has not been fully appreciated and is not regularly considered and applied in therapy.

Hippocrates was first to emphasize seasonal variations in the course of certain diseases when he advised "Whoever wishes to pursue properly the science of medicine must proceed thus. First, he ought to consider what effects each season of the year can produce, for the seasons are not alike but differ widely both in themselves and at their changes. For with the seasons men's diseases, like their digestive organs, suffer change."[1] Today it is well recognized that the natural history of not only infectious diseases but also certain noninfectious diseases, such as hypertension, peptic ulcer, thyroid disorders, dermatitis, burns, rheumatoid arthritis, preeclampsia, disturbances in water and electrolyte balance, chronic bronchitis, multiple sclerosis, chronic asthma, and coronary thrombosis is often modified by fluctuations in climate. Despite this knowledge, the science of medical bioclimatology has lagged and very little attention has been directed to the role of climate and immediate environment in the management of various human maladies.

A study of the influence of climate on human disorders, particularly those of the heart and peripheral circulation, has been in progress for more than 25 years at the cardiovascular laboratories of the Department of Medicine of Tulane University School of Medicine. Extensive investigations on normal and diseased man have not only impressed on us the importance of considering the role of changes in the climate in understanding the pathogenesis of various disorders but has also provided simple and important measures in management.

Our studies have been concerned mostly with hot and humid environments and their effect on the cardiovascular system. During such studies it has become apparent that not only patients with heart disease but also those with chronic renal disease, cerebrovascular disease, debilitated states, malnutrition, electrolyte disturbances, bronchial asthma, hyperthyroidism, exfoliative dermatitides, widespread eczema, and other skin diseases tolerate heat poorly and experience exacerbation of their illness and discomfort under such environments. The effects of cold and damp climate on chronic bronchitis and various arthritides have been studied in Europe. The study by the Royal College of Physicians in England concerning accidental hypothermia and the high mortality rate resulting from it leaves no doubt that extremes of cold climate are not good for health, particularly in people who are old and feeble.

The process of acclimatization at either end of the extremes of temperature benefits normal man, but it is certainly not so effective in diseased states. Change of macroclimate, i.e., change of place for a better and more suitable climate, is sometimes advised by the practicing physicians in the management of certain diseases, but this often might be inappropriate and inadvisable for financial, social, and other reasons.

Recent advances and progress in modern engineering has obviated to a great extent the necessity of change in macroclimate by making it possible to maintain a stable ideal microclimate for comfortable living at comparatively lesser cost. At the same time this has posed the question of defining an ideal climate. Despite the past 25 years of work, it has not been possible for us to establish precise criteria for such an ideal climate; however, our studies have indicated to us that a temperature of 78° F. (25.6° C.) in summer and 75° F. (23.9° C.) in winter with relative humidity of less than 60 per cent can be considered very near to "ideal" for subjects at rest. Variation in clothing, physical activity, and food intake may influence individual differences. Such an ideal microclimate can be obtained by adequate use of fans and air conditioning at home, in vehicles, in offices, and in hospitals.

Over 75 per cent of the United States is warm and uncomfortable in the summer despite widespread use of central air conditioning, one can appreciate discomfort on occasion because the central air conditioning may not produce a uniform and desirable effect in all parts of the building. For this

reason, there is need to consider air conditioning the immediate environment as an adjunct in management of sick patients. This simple measure has impressed on us how much air-conditioned comfortable oxygen tents in the hospital ward and at home can be of benefit to the sick, especially patients in congestive heart failure.

In view of our clinical studies as well as those of others, it has become quite apparent that consideration of a comfortable climate is an important factor in the proper management of patients. This fact should not be underestimated and physicians should never fail to prescribe proper climates in the management of sick people.

G. E. Burch, M.D.
A. Ansari, M.D.
Department of Medicine
Tulane University School of Medicine
New Orleans, La.

REFERENCES

1. Hippocrates: The Loeb Classical Library, New York, 1931, Putnam Sons.
2. Burch, G. E.: Normal and abnormal physiologic effects of tropical climate, New Orleans M. & S. J. 98:14, 1945.
3. Burch, G. E., and DePasquale, N. P.: Hot climates, man and heart disease, Springfield, Ill., 1962, Charles C Thomas Publisher.
4. Report of the Committee on Accidental Hypothermia, Royal College of Physicians of London, 1966.
5. Burch, G. E., and Ansari, A.: Tropical climate, man and heart disease. In press.
6. Burch, G. E., DePasquale, N. P., and Hyman, A. L.: Influence of temperature and oxygen concentration in oxygen tents. Cardiac work in patients with and without congestive heart failure, J.A.M.A. 1 6:1017, 1961.

Book reviews

CARDIAC RADIOLOGY. By Edward F. Dunne, M.B., B.Ch., Philadelphia, 1967. Lea & Febiger Publisher. 256 pages. Price $12.50.

Doctor Dunne has been interested in cardiac radiology during the past 10 years and has examined radiologically almost 2,000 patients with acquired and congenital heart disease. This experience constitutes the basis of this book. The presentation is clear, the radiograms are nicely illustrated, and the legends are not only concise but relevant. The book is short and useful for students, interns, residents and physicians who are not yet cardiologists or radiologists. The list of references can be useful to those who wish further information and greater details. This book is recommended to students and other beginners.

LE CHRONOCARDIOGRAMME. By H. Warembourg and P. Dubar. Paris, France, 1967. L'Expansion Scientifique Francaise. 186 pages.

The term chronocardiogramme is used in this book to designate the simultaneous recording of the ECG (Lead II), phonocardiogram P.C.G., and the left carotid arterial pulse by means of a piezographic device. Employing this technique, the authors claim to be able to evaluate the following parameters of cardiac dynamics: (1) electromechanical systole, (2) expulsion time, (3) tension time, (4) hemodynamic quotient, (5) ventricular transformation time, (6) pressure rise time and (7) diastole duration. These measurements are made without venipuncture or operative procedure. The method was applied to selected cases of valvular heart disease, arrythmias, cardiac failure, chronic cor pulmonale, and congenital heart disease. Other noncardiac diseases were also studied, ... various thyroid, adrenal, pituitary and hepatic problems.

The authors maintain that most cardiac diseases modify the chronocardiogramme in such a way as to (1) aid in reaching accurate diagnosis in difficult cases and (2) providing accurate data about cardiac dynamics without resorting to the classical techniques utilized in the catheterization laboratory. Further, the risk to patient is nil.

The validity of these claims remain to be conclusively demonstrated. The technique is interesting, however and the authors attempts to revise previous methods and interpret them in the light of their experience results in an interesting but speculative addition to the medical literature.

FACTORS INFLUENCING MYOCARDIAL CONTRACTILITY. Edited by Ralph D. Tanz, Fred Kavaler and J. Roberts, New York, London, Academic Press, Inc., 693 pages. Price $28.00.

This is a summary of the proceedings of a conference of the Cardiac Muscle Society held in August, 1966. The monograph is excellent and should be useful to all physiologists, pharmacologists, and cardiologists who were not in attendance at the meeting. Those who follow the literature closely will find practically all of the data very familiar. Nevertheless, it is extremely useful to have the material together in a single volume. The critical reader will find that the monograph readily displays the large gaps in our knowledge of myocardial function, both in health and in disease. The conference dealt with mechanical, electrical, biochemical, and anatomic aspects of heart muscle function. This is a good book which deals rather extensively on a most important subject.

CORONARY CIRCULATION AND ENERGETICS OF THE MYOCARDIUM. Edited by G. Marchetti and B. Taccardi, Basel, Switzerland, 1967. S. Karger AG. 320 pages. Price $18.00.

This represents the proceedings of an International Symposium held in Milan, Italy. The 5 sessions were concerned with regulation of the coronary circulation (sessions), catecholamines and coronary circulation, metabolism of the heart, and coronary insufficiency. As with all symposia, most of the presentations are not new. The discussions are interesting, especially those appended to the various papers. The proceedings represent a fine collection of papers on an extremely important subject in medicine. Not only anatomists, physiologists, biochemists and pharmacologist should find this book valuable but so should cardiologists. Like any symposium, this one indicates more problems than it solves. Unfortunately the presentations are not very critical. The authors in the main merely present aspects of their already published work, a great deal of which is not critically done and the possible errors and deficiencies not indicated. Nevertheless, everyone beginning a study of myocardial function should review this book.

CATECHOLAMINES IN CARDIOVASCULAR PHYSIOLOGY AND DISEASE. Published by the American Heart Association, Inc., New York, 1968. 161 pages. Price $3.00. SYMPOSIUM ON CORONARY HEART DISEASE. Published by the American Heart Association, Inc., New York, 1968, 161 pages. Price $3.00.

These monographs have appeared as supplements to Circulation Research and Circulation, respectively. Therefore, they have already been read by many investigators and clinicians. They are now available as special monographs of the American Heart Association. They are both good monographs which should be included in any good library of Cardiology and Cardiac Physiology.

AORTIC STENOSIS. By Per Fritz Hansen. Copenhagen, 196 . Munksgaard.

This monograph is thoroughly and well written. The text is clear, the illustrations good, and the bibliography fairly extensive, though far from

complete. The author has divided his book into 10 chapters concerned with terminology etiology diagnosis symptoms, signs, hemodynamic changes, electrocardiography roentgenology and prognosis. The presentations are based upon a study of 56 patients and a review of the literature. The discussions are not very critical, however For example, the hemodynamic recordings published are accepted without reservation as to accuracy of the methods used fidelity of recorders and catheter and other errors. Nevertheless, this is a good monograph on an important subject.

HOW TO INTERPRET ELECTROCARDIOGRAMS IN TERMS OF VECTORS. A PRACTICAL MANUAL. By Emanuel Goldberger M D F.A.C.P Springfield, Ill. 1968, Charles C Thomas, Publisher 187 pages. Price $10.50

D Goldberger presents in a *few* pages and in simple form the concept of vectors and vectoranalysis as pplied to the electric events associated with the heart beat. H discusses principles, the normal and abnormal, and som of the lead systems The illustrations are clear and well chosen. Beginners will find this book very useful but, as would be expected, not new in content. The author has selected reference systems and papers from the literature which conform with his own concepts. Although this is acceptable, the less informed reader should be ware of the extreme lack of completeness of the survey by Dr Goldberger of the subject. The bibliography of course, is short and the discussions of the normal and abnormal extremely superficial. For example, the variations of the normal with age and the changes with growth and development are not discussed W th these facts in mind the beginner will find this book to be a good start in learning vectorcardiography

Books received

DIE VERTEILUNG DER LUNGENDURCHBLUTUNG BEIM CHRONISCHEN EMPHYSEM. Ein Beitrag Zur Methodik der Verteilungstorung By H. P Gurtner Bern, 1968 Verlag Hans H ber 186 pages.

EXERCISE TESTS IN RELATION TO CARDIOVASCULAR FUNCTION Report of W H.O Meeting World Health Organization Technical Report Series, N 388 Geneva, 1968 W H. O 30 pages Price $ 60

INTERNAL MEDICINE, based on mechanisms of disease. By Peter J Talso St. Louis 1968 The C. V Mosby Company 797 pages, Price $17.50

OPEN HEART By Nicolai Amosoff New York 1968, A Ballatine Book, 221 pages, Price $.75

CARDIOVASCULAR SURVEY METHODS. By G. A Rose and H Blackburn, Geneva, 1968 World Health Organization, 188 pages, Price $5.25

COOPERATIVE STUDY ON CARDIAC CATHETERIZATION. American Heart Association Monograph No. 20 edited by E. Bra nwald and H J C. Swan, New York, 1968 American Heart Association, 113 pages, Price $5.00

HOCHDRUCK THERAPIE. Symposion uber 2-(2, 6-Dichlorphenylamino)-2-imidazolin-hydrochlorid am 20 and 21 Oktober 1967 in Ulm. By L. Heilmeyer *H. J Holtmeier and E. F Pfeiffer* Stuttgart, 1968, Georg Thieme Verlag, 259 pages.

LOS REFLEJOS DEL CEREBRO. By I M Sechenov with M V Shateralkov H vana, 1965, Academia de Ciencias, 230 pages.

MEDICOS Y MEDICINA EN CUBA. By Emilio Roig de Leuchsenring Havana, 1965, Museo Historico de la Ciencias Medicas, 269 pages.

THE OSCILLOMETRIC VECTORCARDIOGRAM. By Tadowsky and Morris, Springfield, Ill., 1968 Charles C Thomas, Publisher 339 pages, Price $30.00.

STRESS AND DISEASE, ed 2. By Harold G. Wolff, revised and edited by Stewart Wolf and Helen Goodell, Springfield, Ill., 1968 Charles C Thomas, Publisher 277 pages, Price $10 00.

TOXICITY AND ADVERSE REACTION STUDIES WITH NEUROLEPTICS AND ANTIDEPRESSANTS. By H E. Lehmann and T A. Ban with E. Kingston, A. S. Macpherson, and A. St. Jean, Quebec, 1968 Quebec Psychopharmacol. Res. A., 184 pages, Price $2.00

THE BLOOD IN DISEASE. By Charles A. Hall, Philadelphia, 1968 J B. Lippincott Company 292 pages. Price $16.75

MODERN TREATMENT Vol. 5 No. 2, March 1968, (1) Treatment of Parkinson Disease and Allied Disorders by Warren V H ber (2) Treatment of Acquired Hemorrhagic Disorders by Oscar D Ratnoff New York, 1968 Paul B Hoeber Inc., Medical Book Division of Harper and Row Publishers, Inc. 1,500 pages per yea Price $16.00 per year

MODERN TREATMENT Vol. 5 No. 3 May 1968, (1) Treatment of Gallbladder Disease by James B. Carey J (2) Treatment of Menopausal Problems by Eugene J Cohen, New York, 1968 *Paul B.* Hoeber Inc., Medical Book Division of Harper and Row Publishers Inc. 1 500 pages per year Price $16.00 per year

SHOCK—INITIAL MANAGEMENT OF THORACIC AND THORACO-ABDOMINAL TRAUMA. Ed. 2. By Thomas H. Hewlett, Springfield Ill., 1968, Charles C Thomas, 130 pages. Price $11.00.

American Heart Journal

February 1969 Volume 77 Number 2

Editorial

Oral contraceptives and thromboembolic disease

M P Vessey M.B B S
London England

The first report in the medical press of a woman developing a thromboembolic disorder while taking an oral contraceptive preparation appeared in 1961 In that same year two young Los Angeles women using oral contraceptives suffered fatal pulmonary embolisms. Since that time hundreds of similar case histories, relating both to fatal and nonfatal illnesses, have been published in medical journals, and thousands more have been reported to the Food and Drug Administration in the United States and the Committee on Safety of Drugs in Great Britain. The majority of these reports relate to deep-vein thrombosis in the lower limbs or pulmonary embolism but the occurrence of coronary thrombosis, cerebrovascular accidents, mesenteric and other arterial thromboses, and the Budd-Chiari syndrome has also been described

All these conditions also occur in young women who do not use oral contraceptives and in themselves the case reports provide no significant evidence that oral contraceptives are a cause of thromboembolic disease A number of attempts have however been made over the years to assess the problem in a methodical way

In 1962 at a conference sponsored in Chicago by G D Searle and Co. a comparison was made between the reported incidence of episodes of thromboembolic disease in users of Enovid and the incidence in the general population estimated from the results of a number of different studies. The participants recognized the considerable inadequacies of the data available to them but concluded that there was no evidence that Enovid was a cause of thromboembolic disease.

In 1963 a committee appointed by the Food and Drug Administration reviewed about 350 reports of thromboembolic disease in women using Enovid drawn from their own records and from those of the manufacturer On this occasion, existing statistics about the morbidity from thromboembolism in the general population were considered to be unreliable, and the Committee concentrated on reports of death Among Caucasian women using Enovid deaths from thromboembolic disease were estimated to be 14.1 per million annually compared with 8 4 per million in the general population calculated on the basis of national mortality statistics This difference was not statistically significant, but the Committee took into account the limitations of the data and said that carefully planned controlled prospective studies were necessary before reliable conclusions could be drawn.

In 1965 the Committee on Safety of Drugs[1] reviewed their findings in Great Britain for the previous year Sixteen deaths from thromboembolic disease had been reported among women using oral

From the Medical Research Council' Statistical Research Unit, London, England.

contraceptives whereas on the basis of national mortality statistics, about 13 deaths could have been expected if the use of these preparations was unrelated to the disease. The Committee concluded that there was no evidence that oral contraceptives had a thrombogenic effect but they did draw special attention to the fact that 8 of the 16 reported deaths were from pulmonary embolism whereas only 2 such deaths would have been expected.

Quite apart from the absence of comparable control data in any of the investigations just outlined each one also depends on *reported* episodes of thromboembolism for the calculation of morbidity or mortality rates in users of oral contraceptives. The assumption is, therefore that all or nearly all of the episodes affecting women using oral contraceptives are reported by the responsible physicians. That this assumption is in fact untenable has since been demonstrated both by the Food and Drug Administration and by the Committee on Safety of Drugs. Thus in 1966 the Food and Drug Administration showed that, among the 5 million women estimated to have been using oral contraceptives in the United States in 1965 about 85 deaths from idiopathic thromboembolism would have been expected on the basis of the national mortality rates even if the contraceptives had not produced any extra fatalities. In fact, only 13 such deaths were reported. Similarly in 1966 in the special investigation of mortality from thromboembolism in young women undertaken by the Committee on Safety of Drugs,[7] only 8 of the 53 deaths found to have occurred in women using oral contraceptives were independently reported to the Committee by the responsible physicians.

In 1966 Drill[3] reviewed the results of 6 major clinical trials of oral contraceptives covering many thousands of woman years of exposure. On the basis of various morbidity statistics he calculated that a total of 105 cases of thrombophlebitis would have been observed among the participants in these studies if oral contraceptives were unrelated to the disease. In fact, only 28 cases were noted and Drill concluded that oral contraceptives had no thrombogenic effect. Unless however oral contraceptives protect women from thrombophlebitis, an alternative explanation for these results is that such factors as patient selection, losses to follow up and the inevitable inadequacy of the data used to calculate expected numbers of affected individuals preclude any definite conclusions.

In 1966 American[8] and British[9] groups came independently to the conclusion that the best way to obtain adequate data on the thromboembolism problem within a reasonable length of time would be by means of case-control studies, and the results of 3 British investigations have now been published.

In one study organized by the Royal College of General Practitioners,[10] 29 family doctors interviewed women aged 15 to 49 who had consulted them for an episode of thromboembolic disease and the results were compared with those obtained from 2 control groups matched for marital status and broadly for age and parity. The data were too few for any conclusions to be drawn about cerebral or coronary thrombosis, but the results indicated that the risk of venous thrombosis or pulmonary embolism (venous thromboembolism) was increased sixfold in women who were pregnant or in the puerperium and threefold in women who used oral contraceptives. Three quarters of the women with venous thromboembolism suffered from superficial thrombophlebitis of the legs and the estimates of risk therefore relate principally to this condition.

In a study carried out under the auspices of the Committee on Safety of Drugs and reported by Inman and Vessey,[7] inquiries were made by the Committee's medical field staff about the use of oral contraceptives by women aged 20 to 44 certified as dying in England, Wales, and Northern Ireland during 1966 from pulmonary embolism, coronary thrombosis, and cerebral thrombosis. The results were compared with those obtained for control women selected from the same doctors' practices as those in which the fatalities occurred. It was found that, irrespective of age the risk of death from pulmonary embolism or cerebral thrombosis was increased about eight times in previously healthy women using oral contraceptives. In absolute terms however the mortality rate at

tributable to the use of these preparations was substantially lower among those aged 20 to 34 than among those aged 35 to 44 there being an excess of 1 3 and 3 4 deaths per 100 000 users per annum respectively in these two age groups.

The situation in regard to coronary thrombosis was much less well defined in this investigation and the existence of an association with oral contraceptives has not been established. There was however some suggestion that oral contraceptives might be of etiological significance in coronary thrombosis in women under 35

Vessey and Doll[13] carried out an investigation of married women aged 16 to 40 admitted to hospital during 1964 through 1966 with thromboembolic disease without evident predisposing cause Control patients matched for age parity date of admission and absence of any factor predisposing to thromboembolism were selected and all participants in the investigation were interviewed in their homes. From these data it was calculated that the risk of hospital admission for deep vein thrombosis or pulmonary embolism is about 9 to 10 times greater in previously healthy women who use oral contraceptives than in those who do not. By using national sales data for estimating the frequency of use of oral contraceptives in the general population, it was estimated that about 1 in every 2 000 women using oral contraceptives is admitted to hospital each year with idiopathic venous thromboembolism in comparison with about 1 in every 20 000 women not using them.

Evidence was also obtained in this study to support the suggestion that cerebral thrombosis may rarely be caused by oral contraceptives, but no relationship was found between their use and coronary thrombosis.

All these investigations are of course, subject to the usual defects of case-control studies, but their statistical inadequacies are very much less than those of the earlier studies already reviewed. Considered together they provide very strong evidence that oral contraceptives are a cause of venous thromboembolism In conjunction with other investigations,[15 16] in which physicians have reviewed their total clinical experience over a period of time rather than merely singling out particular case histories for special consideration they provide a good indication that these preparations may also be sometimes implicated in ischemic cerebrovascular disturbances. The evidence for a causal association with coronary thrombosis however is weak.

Recent reviews of national mortality statistics for the thromboembolic diseases in the United States and Great Britain[1 17] have led to the conclusion that trends among women of childbearing age have been paralleled by corresponding trends among men and that vital statistics do not support the suggestion that oral contraceptives cause thromboembolic disease. Vessey and Weatherall[18] however have shown that the British vital statistics for the venous thromboembolic diseases are fully compatible with the estimates of the small mortality attributable to the use of oral contraceptives provided by the investigation carried out by the Committee on Safety of Drugs.[7] No attempt has been made to apply the same calculations to vital statistics for the United States because the British estimates of risk may be totally inappropriate when applied to another country where, for example, spontaneously occurring thromboembolic disease may differ in incidence.

None of the investigations so far described has provided any valid evidence that the risk of thromboembolism is associated with any particular oral contraceptive formulation nor that the risk is associated with duration of use. Dr Doll and this author hope to have some additional information shortly on both these points as we are at present updating our investigation[13] by including patients admitted to hospital during 1967 Data obtained from clinical trials where estrogens have been administered to men with coronary heart disease[1] or cancer of the prostate[19] suggest that the estrogen moiety may be at fault and this idea is supported by the recent observation that puerperal thromboembolism is associated with the suppression of lactation by estrogens.[20]

The epidemiological investigations thus strongly suggest a causal relationship between the use of oral contraceptives and some kinds of thromboembolic disease but the case would be greatly strengthened

if the physiological or biochemical effects of their use were shown to contribute to some part of the disease process A vast and bewildering literature has accumulated relating the use of oral contraceptives to changes in various blood clotting factors[9] including platelet function.[23] Many investigations have yielded conflicting results which is not surprising when the great variety of preparations tested the differing laboratory techniques, the varying periods of exposure among the subjects investigated and in some instances, the small numbers of women studied and the inappropriate controls used for comparative purposes, are taken into account. But even if it is accepted that oral contraceptives do affect blood clotting mechanisms the significance of any alteration in terms of an increased risk of spontaneous thrombosis is very uncertain.

Other workers[22,23] have demonstrated changes in vessel walls and in venous distensibility and blood flow produced by the administration of oral contraceptives in experimental animals and in man. These findings, which seem to have been neglected by some workers, could be of significance in relation to venous thromboembolism

Although no definite relationship between oral contraceptives and coronary thrombosis has been established the work done by a number of groups, especially by Wynn and his colleagues,[16,17] on the effect of oral contraceptives on carbohydrate and lipid metabolism provides some basis for suspecting that such a relationship might exist.

In addition to any further epidemiological information which may yet be obtained from case-control studies, at least four prospective investigations of women using oral contraceptives and control subjects have been or are in the process of being established Of these, two are in Great Britain (one organized by the Royal College of General Practitioners and the second jointly by the Medical Research Council and the Family Planning Association) one in the United States (organized by the Kaiser Permanente Medical Care Program) and one in Australia (organized by the Australian College of General Practitioners) It is likely to be 2 or 3 years at least before any of these investigations has anything useful to add to our knowledge of the relationship between oral contraceptives and thromboembolic disease.

Addendum

Since this editorial was submitted, an *article on the same subject, but with different conclusions*, has appeared in the Journal of the American Medical Association (Drill V A and Calhoun D W Oral contraceptives and thromboembolic disease, J.A.M.A. 206 77 1968) Space precludes any discussion of that article here and it must suffice to say that nothing it contains has caused this author to revise the views presented above

REFERENCES

1 Jordan, W M Pulmonary embolism, Lancet 2 1146, 1961
2 Tyler E. T Oral contraception and venous thrombosis, J A M A. 185 131 1963
3 Thromboembolic phenomena in women, Chicago conference 1962, G. D Searle & Co.
4. Final report on Enovid by the ad hoc committee for the evaluation of a possible etiologic relation with thromboembolic conditions, Washington, 1963 Food and Drug Administration.
5 Cahal D A Safety of oral contraceptives Brit. M J 2 1180 1965.
6. Report on the oral contraceptives, Advisory committee on obstetrics and gynecology Washington, 1966 Food and Drug Administration
7 Inman, W H W and Vessey M P Investigation of deaths from pulmonary coronary and cerebral thrombosis and embolism in women of childbearing age, Brit. M J 2:193 1968.
8 Drill, V A. Oral contraceptives, New York, 1966 McGraw Hill Book Company Inc.
9 Medical Research Council Risk of thromboembolic disease in women taking oral contraceptives, Brit. M J 2:355 1967
10. Royal College of General Practitioners Oral contraception and thromboembolic disease J Roy Coll Gen. Practit 13:267 1967
11 Vessey M P and Doll, R Investigation of relation between use of oral contraceptives and thromboembolic disease, Brit M J 2 199, 1968.
12. Ilis, L., Kocen, R. S., McDonald W I and Mondkar V P Oral contraceptives and cerebral arterial occlusion, Brit. M J 2 1164, 1965
13 Shafey S., and Scheinberg, P Neurological syndromes occurring in patients receiving ynthetic steroids (oral contraceptives) Neurology 16:205 1966
14 Bickerstaff E. R., and Holmes, J M Cerebral arterial insufficiency and oral contraceptives, Brit M J 1 726, 1967

15. Cole M : Strokes in young women using oral contraceptives, Arch. Int. Med 120:331 1967
16 Swyer G. I. M Oral contraceptives, thrombosis, and cyclical factor affecting eins, Brit. M J 1:355 1966.
17 Clinical aspects of oral gestogens, Tech R port Series, W H O No. 326 1966.
18. Vessey M P and Weatherall, J A. C Venous thromboembolic disease nd the use of oral contraceptives, Lancet 2:91 1968
19 Oliver M F Thrombosis and estrogens, Lancet 510, 1967
20. Bailar J C., III Thromboembolism and estrogen therapy Lancet 2:560, 1967
21 Daniel D G., Campbell, H and Turnbull, A. C Puerperal thromboembolism and suppression of lactation, Lancet 2:287 1967
22 Bolton C H Hampton J R and Mitchell, J R. A. Effect of oral contracepti agents on platelets and plasma-phospholipids, Lancet 1 1336, 1968.
23 Danforth M Maralo-Estrella P and Buckngham, J C. The effect of pregnancy and Enovid on the rabbit vasculature Am. J Obst. & Gynec. 88:952 1964
24 Goodrich, S. M and Wood J F Peripheral venous distensibility and elocity of enous blood flow during pregnancy and during oral contraceptive therapy Am J Obst & G nec. 90 740, 1964
25 Newstadt, A., Schwartz, R W and Schwartz, S. I Noreth nodrel ith mestranol and enous blood flow J A M A. 198 784 1966.
26. Wynn, V and Doar J W H Some effects of oral contraceptives on carboh drate metabolism Lancet 2 715, 1966
27 Wy n, V Doar J W H., and Mills, G L. Some effects of oral contraceptives on serum lipid and lipoprotein levels, Lancet 2 720, 1966.

Clinical communications

Unusual occurrence of nonaberrant conduction in patients with atrial fibrillation and aberrant conduction

Hein Wellens, M.D.
Amsterdam, The Netherlands

The occurrence of non- or less aberrant conduction after a short RR interval in a patient with atrial fibrillation who shows aberrant conduction after longer RR intervals is a rare finding. Recently 2 patients showing this phenomenon were seen. This article gives a description of their electrocardiograms (ECG's) and presents a few hypotheses to explain this finding.

Case reports

Case 1. A 74-year-old housewife (Patient A) was admitted to our department for evaluation of attacks of palpitations. Apart from these attacks, she did not have any complaints. On admission, the ECG (Fig. 1) showed a low voltage tracing with a sinus rhythm. There was an incomplete right bundle branch block (rsr' complexes over the right precordium) and notched QRS complexes in Lead III and V.

A few days later during an attack of palpitations the following tracing was obtained (Figs. 2 and 3). The rhythm now was atrial fibrillation with a ventricular rate of 120 to 160 per minute.

The QRS complexes showed a complete right bundle branch block with occasional complexes showing the incomplete right bundle branch block pattern as present during sinus rhythm (Fig. 1).

These incomplete right bundle branch block complexes were seen in 2 locations (Fig. 3). (1) Location A terminating a long RR interval. (2) Location B shortly after the end of the T wave of a complete right bundle branch block complex.

The explanation for beats of Type A is clear. less aberrant conduction in beats terminating a long RR interval is a well known finding in atrial fibrillation with bundle branch block. The occurrence of less aberrant conducted complexes terminating a short RR interval in atrial fibrillation is highly unusual.

Possible explanations for this last finding are the following: (1) Ventricular premature beats originating in the septum of the ventricle of the blocked bundle branch. This seems very improbable in view of the absence of fixed coupling or evidence of origin from a parasystolic focus. The strongest argument against it is the similarity of the less aberrant conducted complexes obtained during sinus rhythm. (2) In our opinion 3 hypotheses are much more likely: (a) the less aberrant conducted complexes occur when the impulse from the A-V node travels down the right bundle branch in the supernormal phase of conduction produced by the preceding beat. (b) in the right bundle branch 2 separate pathways are present with different properties as far as conduction velocity and refractoriness is concerned. (c) in the right bundle branch 2 successive zones are present with different properties in conduction velocity and refractoriness. See discussion for a detailed description of these hypotheses.

Case 2. A 64-year-old housewife (Patient B) was admitted to the Department of Medicine for the treatment of hyperthyroidism and paroxysmal atrial fibrillation.

On admission, the ECG showed atrial fibrillation with a ventricular rate of 110 to 140 per minute. A complete left bundle branch block configuration was present but a few complexes did not show conduction delay in the left bundle branch (Fig. 4). These complexes were seen in 2 locations (Fig. 3). (1) Terminating a long RR interval (Type A). (2) Shortly after the end of the T wave of a complete left bundle branch block complex (Type B).

From the Department of Cardiology and Clinical Physiology, University of Amsterdam, Wilhelmina Gasthuis, Amsterdam, The Netherlands.
Received for publication Jan. 26, 1968.

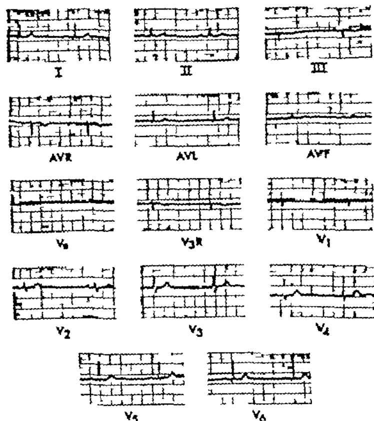


Fig. 1 In Patient A, the ECG shows sinus rhythm low voltage and an incomplete right bundle branch block (rSr' configuration in V3R and V1).

This tracing looked very similar to the ECG of Patient A, the only difference being that here aberrant conduction took place in the left bundle branch. A strong argument was furnished by comparing the tracing with one obtained in another hospital 3 months prior to her current admission. This ECG although incomplete and without standardization, showed sinus rhythm with part f om a different voltage, completes similar to the normal complexes seen during atrial fibrillation (Fig. 6).

Discussion

The ECGs obtained during atrial fibrillation in both patients showed nonaberrant conduction after a short RR interval while after longer and shorter RR intervals aberrant conduction took place. Possible explanations for this finding are (1) the presence of a supernormal phase of conduction in one of the bundle branches (2) longitudinal dissociation within one bundle branch (3) the presence in one bundle branch of 2 consecutive zones with different properties.

The presence of a supernormal phase of conduction in one of the bundle branches Historically this should be presented first as it was demonstrated to be present in the isolated nerve preparation as early as 1913. In 1962 Pick and associates[3] and Lepeschkin and Kimura[4] reviewed the literature on the occurrence of a supernormal phase of A V conduction in clinical electrocardiography and added several cases of their own. Recently the introduction of electrical stimulation of the ventricle in total heart block gave new findings in favor of the presence of a supernormal phase in the A V conduction system. Still the width and the exact localization of the supernormal phase is unknown and definite electrophysiological evidence for its existence are lacking.

Most writers believe it to be situated closely before the end of the T wave. Very rare indeed, are reports dealing

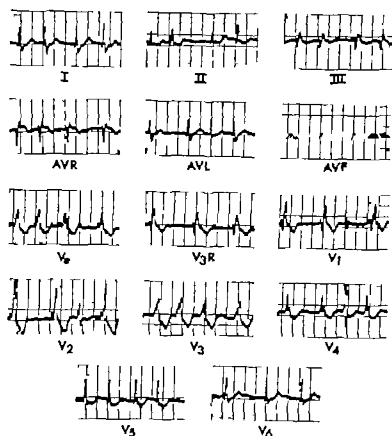


Fig. 2. I Patient A, the ECG shows atrial fibrillation. The QRS complexes have complete right bundle branch block configuration, b t occasionally smaller QRS complexes are seen. For detailed discussion see Fig 3.

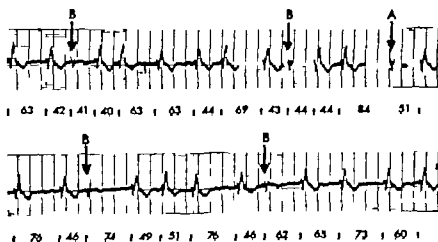


Fig. 3 Continuous trip of Lead V of Patient A. The tracing shows complet right bundle branch block with few omplexes show ng the same configuration seen Fig. 1. The latter complexes are seen in 2 locations. Type A terminating long i terval nd type B, hortly after the end of the T wa of complete right bundle branch block complex. A explained in the text, these type B complexes ca be explained in 3 different ways.

with supernormal conduction in one of the bundle branches.[4-7] Holzmann and Schaub describe 4 cases of supernormal conduction in patients with atrial fibrillation with aberrant conduction in one of the bundle branches. Three of their cases showed a right bundle branch block, the other one a left bundle branch block. The "supernormally" conducted beats showed disappearance of the aberrant conduction. Their cases are comparable to ours. The localization and width of the supernormal phase of bundle branch conduction differs in these patients and seems to be primarily determined by the preceding RR interval.

In Patient A supernormally conducted beats occurred 420 to 460 msec. after the beginning of the preceding QRS complex. The RR interval terminated by that QRS complex ranged between 630 to 760 msec. In Patient B we made a graph relating the preceding RR interval to the left bundle branch block beat—nonaberrantly conducted beat interval, assuming that the last preceding RR interval is the prime determinant for the location of the zone where supernormal conduction can take place. From that graph (Fig. 7) it can be seen that with a longer preceding RR interval the area for supernormal conduc

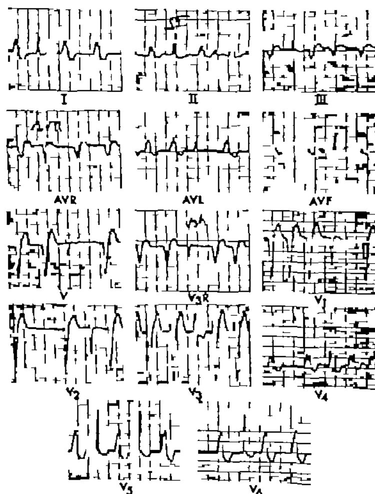


Fig. 4. In Patient B the ECG shows atrial fibrillation with complete left bundle branch block. Occasionally complexes without aberrant conduction are seen. The ECG was taken after the patient was digitalized. For detailed discussion see Fig. 5.

tion comes later and also becomes wider In this patient, supernormal conduction in the left bundle branch took place 420 to 560 msec after the preceding QRS complex. The RR interval terminated by that QRS complex ranged from 360 to 860 msec At a preceding RR interval of 600 msec, supernormal conduction was present 460 to 530 msec following that RR interval It is clear that the chance for the impulse to fall into the supernormal phase of conduction is greater when that phase is wider due to a longer preceding RR interval. The occurrence of supernormal conduction in A V bundle branch system has to be regarded as evidence for severe myocardial damage.

Longitudinal dissociation within one bu-

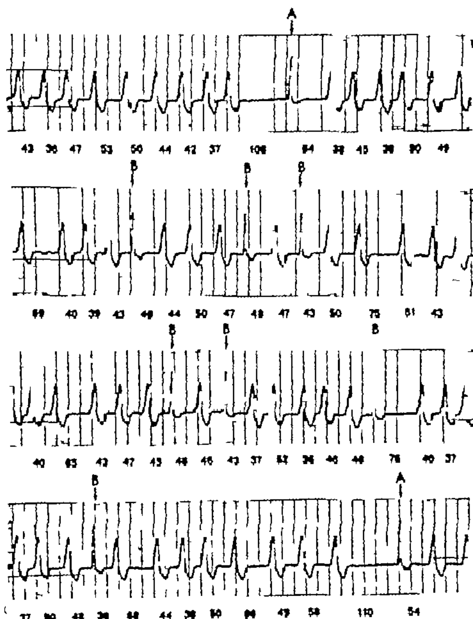


Fig. 5 Continuous strip of Lead V of Patient B, showing atrial fibrillation with complete left bundle branch block. Occasionally smaller QRS complexes showing no aberrant conduction are seen. They are seen in 2 locations. Type A terminating a long interval and type B occurring shortly after a complete left bundle branch block complex. Again, 3 different explanations for the latter complexes can be given. See text.

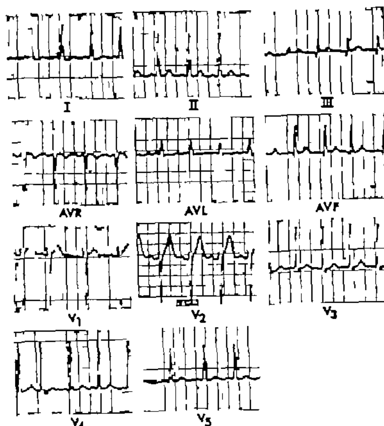


Fig 6 1 Patient B this ECG was taken 3 months prior to Fig 4 Unfortunately it was incomplete, and standardization was lacking The tracing taken during sinus rhythm, however shows QRS complexes that are apart from differences in voltage similar to the nonaberrantly conducted complexes in Figs. 4 and 5.

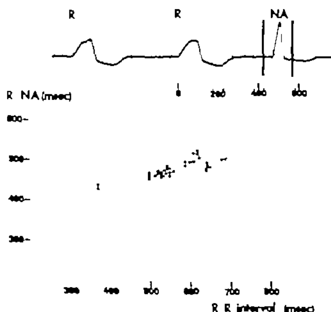


Fig 7 Graph showing the relation between the interval complete left bundle branch block complex—nonaberrantly conducted complex (R to NA interval) versus the RR interval of the 2 complete left bundle branch block complexes immediately preceding the nonaberrantly conducted beat. For the measurements, Lead V was written at paperspeed of 100 mm. per second, as demonstrated in the top half of this figure. The 2 bars surrounding the nonaberrantly conducted complex indicate the zone where related to the preceding RR interval nonaberrant conduction took place. This zone is 140 msec. wide (420 to 560 msec. after the preceding aberrantly conducted complex, the preceding RR intervals ranging from 360 to 860 msec.).

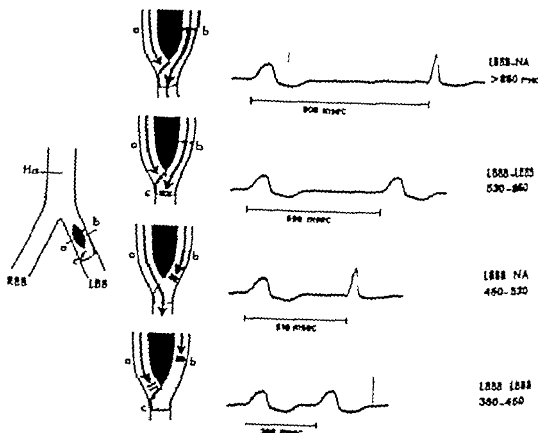


Fig. 8. Longitudinal dissociation in the left bundle branch explaining how after a preceding RR interval of 600 msec (1) nonaberrant conduction takes place when the next QRS comes more than 860 msec later (LBBB to NA); (2) left bundle branch block complexes occur when this period lies between 530 and 860 msec (LBBB to LBBB); (3) nonaberrant conduction in the period 460 to 530 msec (LBBB to NA) and (4) again left bundle branch block configuration is seen when the interval becomes less than 460 msec (LBBB to LBBB). See text for more detailed explanation.

dle branch. Recent work in our department by Durrer and Schulenburg and reported by Durrer[4] suggests that 2 separate pathways in the A-V node might be the explanation for the finding in a patient of a gap in antegrade A-V conduction during regular driving of the atria with atrial premature beats at decreasing delays.

Evidence for the presence of longitudinal dissociation in the A-V node has been presented by Scherf and Moe and Mendez,[1] especially in the explanation of reciprocal rhythms. In one bundle branch a fibrotic or dead zone might cause a split in this bundle thereby producing 2 pathways. By assuming that these 2 pathways differ in their properties as far as length, conduction velocity and refractoriness is concerned, a longitudinal dissociation within the bundle branch results. In Fig. 8 the left bundle branch (the same explanation holds for the right bundle branch) is divided by a dead zone into pathway A and B.

They come together again at C. In our cases we have to assume (1) that pathway A is longer than B and (2) in pathway B a zone with a long refractory period and decreased conduction is present (shaded area). The area where A and B join (shaded area C) also has an increased refractory period and decreased conduction.

In this way the ECG of Patient B can be explained as follows. (For the sake of clarity the interval preceding the interval to be discussed is kept constant at 600 msec realizing that the intervals discussed below change with the preceding RR

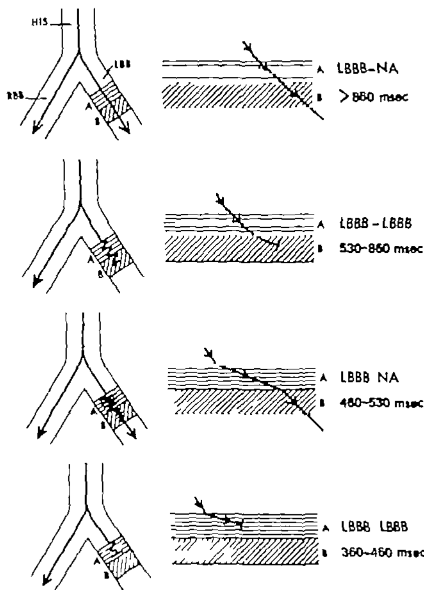


Fig. 9. T consecutive zones A nd B with different properties in one bundle branch. Shown here is location in the left bundle branch. Depending upon the interval between the foregoing aberrantly conductive complex the next complex (1) passes through the left bundle branch (interval longer than 860 msec), (2) is blocked the left bundle branch (interval between 530 nd 860 msec), (3) passes through the left bundle branch (interval between 460 and 530 msec.), (4) is blocked in the left bundle branch (intervals shorter than 460 msec) Again, the RR interval preceding the interval discussed under 1 to 4 is 600 msec.

interval.) (1) At an interval longer than 860 msec nonaberrant conduction is taking place The explanation being that the impulse travels down pathway B and passes through area C without difficulty The impulse traveling through pathway A arrives at C when this is refractory from the impulse from pathway B ( ) At intervals between 530 and 860 msec the impulse traveling down pathway B is conducted with decrement in the shaded area, comes to a halt in area C The impulse going down pathway A due to the fact that this pathway is longer than B arrives at C when this is made refractory by the decrementally conducted impulse of path-

way B The result is a QRS complex with left bundle branch block configuration. (3) At intervals between 460 and 530 msec. the impulse traveling down pathway B comes to a halt at a level above area C Now the impulse from path A can go through C with a normal looking QRS complex as a result. (4) At intervals between 360 and 460 msec the impulse traveling down A reaches C when this is still refractory from the foregoing impulse The QRS complex now has a left bundle branch block configuration

The presence in one bundle branch of 2 consecutive zones with different properties (transversal dissociation) This possibility has been described for the A V node by Moe and Mendez Fig 9 illustrates this concept In the left bundle branch zones A and B are present. Both zones have decreased conduction velocity and refractoriness as compared to the right bundle branch These properties, however are not the same in zones A and B Again, we assume that the RR interval preceding the interval to be discussed is 600 msec (1) At long intervals (> 860 msec.) conduction goes through both left and right bundle branch resulting in nonaberrant conducted QRS complexes. (2) At shorter intervals (530 to 860 msec.) the impulse travels through zone A to be blocked in zone B the latter tissue being refractory Normal conduction takes place in the right bundle branch. The QRS complex zone shows a left bundle branch block configuration (3) At further shortening of the interval the impulse is slowed down so much in zone A that it reaches zone B when this is no longer refractory So now the impulse passes through the left bundle branch again. In this situation due to the slowing in zone A one should expect a QRS complex not completely identical to the one occurring after an interval of more than 860 msec. but one showing a small amount of left aberrant conduction unless a similar degree of slowing takes place in the right bundle branch (4) At the shortest intervals (360 to 460 msec.) the impulse is already blocked in zone A of the left bundle and passes through the right bundle resulting in a left bundle branch block configuration of the QRS complex.

In our patients, we did not find differences in the QRS configuration of the nonaberrant conduction complexes in situations 1 and 3 So this explanation seems rather unlikely in our cases, unless concomitant slowing in the right bundle branch takes place at shorter intervals.

Summary

A description is given of the ECG's of 2 patients, who during atrial fibrillation, showed nonaberrant conducted complexes at short RR intervals and aberrant conducted complexes at shorter and longer RR intervals. A few hypotheses for the explanation of this phenomenon are offered

The author is indebted to Prof Durrer and Drs G E Freud and M J Janse for their help and advice in the preparation of this article.

REFERENCES

1 Adrian, E. D and Lucas, K. On the summation of propagated disturbances in the nerve and the muscle, J Physiol. 44:68, 1912.
2 Pick, A., Langendorf R and Katz, L N The supernormal phase of atrioventricular conduction Circulation 26:388, 1962
3. Lepeschkin, E., and Kimura, E. The supernormal phase of atrio-ventricular conduction, Proc. IV Internat. Congr Cardiol. II 114 1962
4 Burchell H. B Analogy of electronic pacemaker and ventricular parasystole with observation on refractory period, supernormal phase and synchronization, Circulation 27:878, 1963
5 Scherf D and Scharf M. M Supernormal phase of intraventricular conduction, Am. Heart J 36:621 1948.
6 Contro, S., Magri, G., and Nuti ll, G. Premature beats overcoming impaired intraventricular conduction. Supernormal phase of intraventricular conduction, Am. Heart J 51:372, 1956.
7 Holzmann, M., and Scherb, F Beobachtungen zur übernormalen Phase bei Schenkelblock. Cardiologia 33:84 1958.
8. Durrer D Third Thomas Lewis Lecture Cardiovas. Res., 2 1, 1963
9 Scherf D : An experimental study of reciprocating rhythm, Arch. I t. Med. 67:372, 1941
10. Moe, G., and Mendez, C. The physiologic basis of reciprocal rhythm, Progr Cardiovas Dis 8:461 1966.

Cardiac tamponade during cardiac catheterization

Management by immediate pericardiostomy and drainage

Andrew G. Morrow, M.D.
Robert L. Reis, M.D.
John Ross, Jr., M.D.
Bethesda, Md.

Acute cardiac tamponade is most frequently encountered in young individuals without pre-existing cardiac disease who have sustained penetrating wounds of the heart. In such patients, the clinical manifestations of tamponade and the methods of surgical management are now well recognized. When tamponade is evident, aspiration of the blood usually results in immediate and often dramatic circulatory improvement. If tamponade recurs, pericardiocentesis may be repeated until the bleeding ceases; if bleeding persists, thoracotomy and suture of the cardiac wound become necessary.

Cardiac tamponade may also occur in the course of diagnostic cardiac catheterization, but in this clinical setting the methods of management outlined above are sometimes ineffective, a fact attested by the deaths from recognized tamponade which have occurred in this and other diagnostic laboratories.[-4] When cardiac tamponade occurs during catheterization the patient almost invariably is one who has serious congenital or acquired heart disease and impaired cardiac performance, conditions which greatly augment the deleterious effects of restricted ventricular filling. Unless the tamponade is recognized promptly and relieved completely, irreversible circulatory failure may ensue. On the other hand, such patients tolerate repeated pericardial aspirations poorly, and thoracotomy for suture of a cardiac wound is associated with an unusually high risk because of the underlying cardiac disease.

With the above considerations in mind a new method of management of acute cardiac tamponade resulting from cardiac catheterization was adopted at the National Heart Institute, in 1963. The plan, devised on a prospective basis, was based on 2 premises: (1) that bleeding will cease spontaneously from a perforation or laceration of any cardiac chamber which is inflicted by a cardiac catheter or needle, and (2) that effective and continued decompression of the heart can best be achieved by open pericardiostomy and drainage of the pericardial space.

Subsequent to the adoption of this plan 4 patients who incurred cardiac tamponade at catheterization have been treated by pericardiostomy. The details of their management, and the results of this form of

From the Clinic of Surgery and Cardiology Branch, National Heart Institute, Bethesda, Md. 20014.
Received for publication Feb. 1968.

treatment are described in the report which follows.

Clinical summaries

Case 1. G. O. (04-97-86), a man 51 years of age, was severely symptomatic, and presented the clinical findings of combined aortic stenosis and regurgitation. Right retrograde arterial, and transseptal left heart catheterizations were performed. Some difficulty was encountered when attempts were made to pass the transseptal catheter across the mitral valve and, in retrospect, it was considered that the catheter might have perforated the left atrial appendage. One hour after completion of the procedure the patient became hypotensive, the central venous pressure rose from a normal level to 14 mm. Hg, and fluoroscopic examination revealed increase in the size of the cardiac shadow and diminished cardiac pulsations. The diagnosis of cardiac tamponade was established by the aspiration of 10 c.c. of blood from the pericardial space.

The patient was immediately anesthetized, and the pericardium exposed by resection of the fourth left costal cartilage. When the pericardium was incised, 500 ml. of liquid and clotted blood were evacuated, and the arterial and venous pressures immediately returned to normal levels. A No. 28 rubber drainage tube was inserted into the pericardial space and connected to underwater drainage. 1,000 ml. of blood drained from the tube during the first 2 hours and an additional 400 ml. over the subsequent 20 hours. The blood was replaced, as it was lost, by transfusions. No drainage occurred after 24 hours, and the tube was removed. Antibiotics were administered for 7 days. The patient made an uneventful recovery, and when aortic valve replacement was carried out 6 months later the pericardial space was found to be free.

Case 2. B. W. (04-34-20), a 37-year-old woman had experienced progressive dyspnea, anginal pain, and congestive heart failure. On examination the findings were indicative of idiopathic hypertrophic subaortic stenosis, and right and retrograde arterial left heart catheterizations were carried out. A peak systolic pressure gradient of 110 mm. Hg was demonstrated within the left ventricular outflow tract and the diagnosis of hypertrophic subaortic stenosis was confirmed by a selective angiocardiogram with injection into the left ventricle. Shortly after the left ventricular catheter was withdrawn, the patient became hypotensive and decreased cardiac pulsations, elevated venous pressure, and pulsus paradoxus were evident. Only 4 ml. of blood could be aspirated by pericardiocentesis, after which the patient developed marked hypotension and a further rise in central venous pressure to 20 mm. Hg. Under local anesthesia the left fourth costal cartilage was excised and 300 ml. of fresh blood was evacuated from the pericardial space. The arterial and venous pressures immediately became normal. A soft rubber drainage tube was inserted into the pericardial space and another into the left pleural space, which also had been opened. 280 ml. of blood drained through the tubes during the following 18 hours, after which time the tubes were removed. Antibiotics were administered for 7 days, and the patient recovered without incident. Left ventriculotomy and myectomy were successfully carried out 3 months later.

Case 3. L. L. (06-26-33), a 58-year-old woman had severe symptoms attributable to calcific aortic stenosis and right heart catheterization and anterior percutaneous puncture of the left ventricle were carried out. A peak systolic gradient across the aortic valve of 75 mm. Hg was demonstrated, and a thoracic aortogram revealed no significant aortic regurgitation. One hour after the left ventricular puncture, the patient suddenly became hypotensive, the central venous pressure rose to 40 mm. Hg, and the size of the cardiac shadow enlarged. 100 ml. of blood was obtained by pericardiocentesis. After induction of general anesthesia, the fifth left costal cartilage was resected exposing a distended pericardium. When the pericardium was opened, 400 ml. of blood was evacuated, and the venous and arterial pressures returned to normal. Inspection of the portion of the left ventricle underlying the pericardial incision revealed active bleeding from a marginal branch of the left anterior descending coronary artery which had been lacerated by the percutaneous needle; the artery was ligated. Drainage tubes were inserted into both the pericardial and left pleural spaces. The patient made an uneventful recovery. Aortic valve replacement was performed 3 months later and at this time the pericardium was found to be adherent to the cardiac apex over an area about 2 cm. in diameter.

Case 4. P. R. (07-00-80) is a 35-year-old woman in whom the clinical and electrocardiographic findings suggested the diagnosis of either hypertrophic subaortic stenosis or idiopathic left ventricular hypertrophy without obstruction. She had moderately severe symptoms. Right and transseptal left heart catheterizations were performed, and the studies revealed elevation of both ventricular end-diastolic pressures, but no evidence of ventricular outflow tract obstruction. At the conclusion of the study the patient experienced the sudden onset of severe precordial pain and became hypotensive. The blood pressure rose with the administration of 500 ml. of whole blood, but then fell again, and diminished cardiac pulsations were evident fluoroscopically. Aspiration of the pericardial space yielded 65 ml. of blood, after which the arterial pressure rose but then fell again to an abnormally low level. Under general anesthesia, the left fifth costal cartilage was resected, and 200 ml. of fresh blood was evacuated from the pericardium; venous and arterial pressures immediately became normal. A drainage tube was inserted into the pericardial space; in the ensuing 24 hours, 450 ml. of blood drained from the tube and it was subsequently removed. Antibiotics were administered for 7 days. The patient made an uneventful recovery.

Operative methods

In each of the 4 patients described the occurrence of cardiac tamponade was recognized in the cardiac catheterization laboratory and a surgeon and an anesthesiologist were immediately summoned.

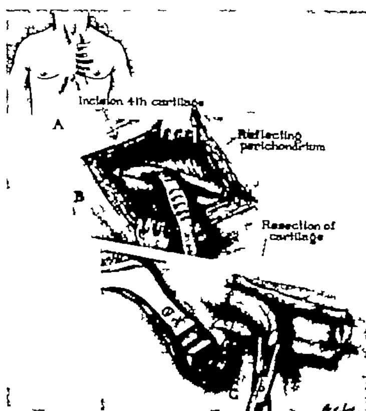


Fig. 1 The operative methods employed for pericardiostomy. An incision is made over the left fourth or fifth costal cartilage (*A*); the perichondrium is incised, the cartilage is freed with periosteal elevator (*B*), and a segment of costal cartilage is resected with rib shear (*C*).

The patients were given assisted respiration with 100 per cent oxygen administered by mask until the necessity of pericardiostomy had been decided upon. In 3 patients, general anesthesia was induced with an intravenous agent, and an endotracheal tube inserted. In Patient B. W. the procedure was performed with local anesthesia. Tracheal intubation generally is desirable, however, to permit positive pressure respiration and inflation of the left lung if the pleural space is opened. The hemodynamic state of the patient with acute cardiac tamponade is, at best, a precarious one and the induction of anesthesia and tracheal intubation should be carried out by an experienced anesthesiologist, and every attempt made to avoid reflex bradycardia and/or hypoxia.

The methods employed for pericardiostomy are illustrated in Figs. 1 and 2. A submammary incision is made over the left fourth or fifth costal cartilage; the incision extends from the sternum to the anterior axillary line. The perichondrium is incised longitudinally and 2 transverse incisions are made at either end of the longitudinal one. The cartilage is freed with a periosteal elevator and a segment 4 to 5 cm. in length is resected with a rib shear (Fig. 1). The pericardium is exposed through the posterior perichondrium and a stellate incision made into it. The intrapericardial blood gushes forth spontaneously and after it is evacuated a soft rubber drainage tube with multiple side holes is inserted into the pericardial space posterior to the heart (Fig. 2). The left parietal pleura is reflected on the pericardium at the lateral extent of the incision and if the pleural space also is entered a second tube is inserted into it. The tubes are connected to underwater drainage.

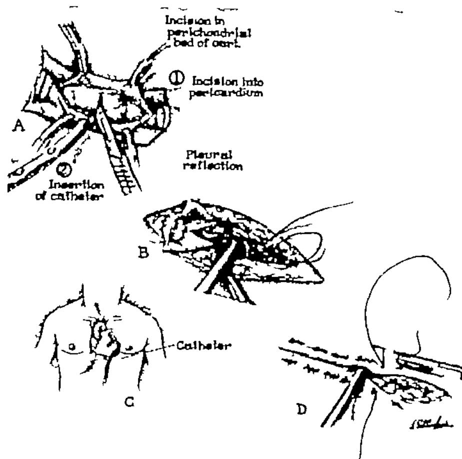


Fig 2 The pericardium is exposed through the posterior perichondrium, stellate incision is made into it, and a t be connected t water-seal drainage is inserted int the pericardial space posterior t the heart. After irrigation and inst llation of antibiotics the wound is closed bout the tube in 2 layers. A second tube is inserted into the pleural space if it has been opened

When effective decompression of the heart is achieved circulatory improvement *is immediate and dramatic. Blood* loss is replaced by transfusion and when the patient s condition is stable he is removed to an operating room The wound which has usually been made under less *than optimal aseptic conditions,* is irrigated with copious amounts of saline penicillin and streptomycin are instilled locally and it is closed about the tubes in 2 layers. In each patient penicillin and streptomycin were administered for 7 days after pericardiostomy and the wounds healed without infection

Comment

The sudden occurrence of severe hypotension during or shortly after cardiac catheterization is a medical emergency which demands immediate and continuing *attention In this setting hypotension* is most often the result of a vaso-vagal reaction and atropine should be administered promptly even if the heart rate is not unduly slow Unless immediate improvement occurs, a vasopressor is given intravenously initially in a single dose then if necessary as a continuous infusion. If hypotension persists or recurs after these measures have been instituted or if a normal systemic arterial pressure can be maintained only by continuing administration of a vasopressor acute cardiac tamponade should be considered likely When cardiac tamponade occurs in the course of cardiac catheterization it usually can be recognized without difficulty since

facilities and equipment are immediately available for monitoring and recording the central venous and systemic arterial pressures and for serial fluoroscopic examinations of the heart.

In the patients described abnormal elevation of the venous pressure, increase in the size of the cardiac shadow and diminished amplitude of cardiac pulsations were uniformly noted and one patient also had pulsus paradoxicus. The diagnosis of pericardial tamponade was confirmed in each instance by the aspiration of fresh blood from the pericardial space and pericardiostomy was performed promptly In one patient (B W) profound and unresponsive circulatory failure necessitated pericardiostomy prior to the administration of general anesthesia or controlled ventilation in the remaining patients general endotracheal anesthesia was instituted prior to the procedure. The site of bleeding was apparent in one patient (L. L.) and the small lacerated coronary artery was ligated In the other patients, the site of cardiac injury was not determined but the pericardiostomy effectively maintained cardiac decompression until bleeding from the cardiac wounds ceased spontaneously Since adoption of the plan of treatment described no patient at the National Heart Institute has died of acute cardiac tamponade incurred at cardiac catheterization.

Summary

When acute cardiac tamponade occurs as a complication of cardiac catheterization the patient is usually one in whom cardiac performance is already impaired and immediate relief of restriction to ventricular filling is mandatory to prevent irreversible circulatory failure Effective decompression of the heart is not uniformly achieved by pericardiocentesis, however and death from recognized tamponade sometimes occurs. Therefore in 4 patients who incurred tamponade during cardiac catheterization immediate pericardiostomy and drainage of the pericardial space was successfully employed The details of the management of these patients, the operative methods utilized, and the rationale for this form of treatment are described

REFERENCES

1 Björck, V O., Cullhed, L, Hallen, A Lodin H. and Malers, E Sequelae of left ventricular puncture and angiocardiography Circulation 24:204, 1961
2. Clinicopathologic conference Rapidly developing aortic insufficiency with progressive cardiac failure, retrograde aortic catheterization and pericardial tamponade, Am. J Med. 37:949 1964.
3. Dalgaard, J B. F tal right ventricular perforation during cardiac catheterization, Acta med scandina 175:697 1964
4 Lurie, P R., and Grajo, M Z Accidental cardiac puncture during right heart catheterization, Pediatrics 29:283 1962.
5 Russell, R. O J Carrol, J F and Hood, W G J Cardiac tamponade. complication of the transseptal technic of left heart catheterization resulting in fatality Am. J Cardiol. 13:558, 1964.

Comparison of thresholds in epicardial and endocardial stimulation of the human heart by chronically implanted pacemaker electrodes

A. D. Overdyk, M.D.
E. Dekker, M.D.
Amsterdam, The Netherlands

The accumulation of data on stimulation thresholds for various types of pacemaker electrodes is of great importance for the management of patients with total heart block and for the proper design of the pacemaker units connected to these electrodes.

The thresholds of epicardial and intramural electrodes tend to rise with time. Surgical trauma during implantation and fixation of the electrodes is thought to contribute to this phenomenon.[1]

Endocardial electrodes, which can be introduced at small operative risk by the pervenous method, are being used at present with increasing frequency. Their use has become the method of choice in many centers. The electrode is gently applied to the endocardium, where it should cause a minimum of surgical trauma. There are no ligatures to cause a tissue reaction. It might therefore be expected that stimulation thresholds are lower and more stable in endocardial electrodes.

In this study results of measurement of stimulation thresholds in chronically implanted endocardial electrodes are reported. A comparison is made with similar measurements in epicardial electrodes.

Methods

Thresholds were measured in 36 patients. All patients in this series were treated for total heart block by implantation of an electronic pacemaker.

Epicardial electrodes. In 12 patients, thoracotomy was performed and 2 to 4 platinum epicardial electrodes (total 31) of the type described by Elmqvist and associates, each with a diameter of 9 mm., were fixed by 3 atraumatic sutures to the surface of the heart. After 12 to 18 months, the pacemaker was exchanged electively or because of pacemaker failure. On this occasion unipolar thresholds for cathodal and anodal stimulation were determined by methods previously described.[2]

Endocardial electrodes. In 24 patients, a Lagergren platinum endocardial electrode was introduced pervenously into the inferior margin of the right ventricle.

Thresholds were measured after 11 to 21 months during pacemaker exchange. The median observation time for the endocardial electrodes was 13½ as compared to 14 months for the epicardial electrodes. At a 5 per cent level of significance no difference in the observation times could be shown. For threshold measurement

Received for publication Feb. 26, 1968.
From the University Department of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam, The Netherlands.

Table I

	Mean threshold M cathodal		*Mean threshold M anodal*	
24 endocardial electrodes	5,8	P < 0.05	7.9	P < 0.05
31 epicardial electrodes	6,8		9.0	

an external pacemaker was used with a pulse duration of 1.8 msec. and a continuously adjustable amplitude. A subcutaneous needle served as the indifferent electrode. The electrocardiogram (ECG) was continuously monitored. The amplitude of the current was adjusted to the minimum value which ensured response of the heart to all pacemaker stimuli.

The stimulating current was then calculated from the maximum voltage appearing over a 100 ohm resistor in series with the patient. Differences between series were assessed by the Wilcoxon test[*,7] at a 5 per cent significance level.

Results

The results of our threshold measurements in 36 patients are summarized in Table I.

The histograms (Fig. 1) stress the considerable spread in threshold values of both types of electrodes. The graphs (Figs. 2 and 3) relate anodal and cathodal thresholds in epicardial and endocardial electrodes.

Discussion

The mean threshold is somewhat lower in endocardial electrodes when compared to epicardial electrodes. The result is at a 5 per cent level indicative of such a difference for both cathodal and anodal stimulation. The magnitude of the difference is however surprisingly small in view of the fact that 2 entirely different approaches to myocardial stimulation have been chosen: epicardial stimulation through a platinum disc electrode fixed by 3 sutures through the ventricular wall and endocardial stimulation through a thin flexible wire carrying a much smaller cylindrical platinum electrode which is atraumatically applied. The fact that the thresholds measured through these 2 entirely different electrodes differ so little is hard to explain. This might be caused by a tissue reaction of approximately equal extent around both electrodes.[13] Lagergren and associates, however found only inconsiderable tissue reaction and virtually no degenerative changes in the muscle cells around the electrodes.

Data on threshold behavior in chronically implanted endocardial and epicardial electrodes are scarce in the literature. Comparison of such data as are available is hindered by the use of different units for expressing threshold values. Expressing unipolar thresholds as volts appearing across the patient has the disadvantage that the results thus given represent the sum of the voltages across the stimulating and the indifferent electrodes. Moreover polarization at the electrodes[7] prevents them from following Ohm's law so that at lower stimulation strengths an increasing proportion of the applied voltage is opposed by the polarization process both at the stimulating and indifferent electrodes.

Expression in joules (volts, amperes, seconds) has unique advantages in studying the economy of pacemaker output at different pulse durations[12,13] but in clinical practice where pulse duration of most commercially available pacemakers is fixed this method is cumbersome. Its exact execution requires the evaluation of the time integral of all instantaneous products of current and voltage during the course of the pulse. Furthermore, it implicitly contains all the disadvantages of voltage measurements. Expression of thresholds in current milliamperes (Ma.) lacks some of these disadvantages. The values can immediately be read off the oscilloscope and made available for surgical decisions to be taken during implantation, revision and replacement of pacemaker units.

For the same practical reasons, all measurements in these studies were taken at the beginning of the pulse where current is at a maximum.

*Medtronic external pacemaker type 5800

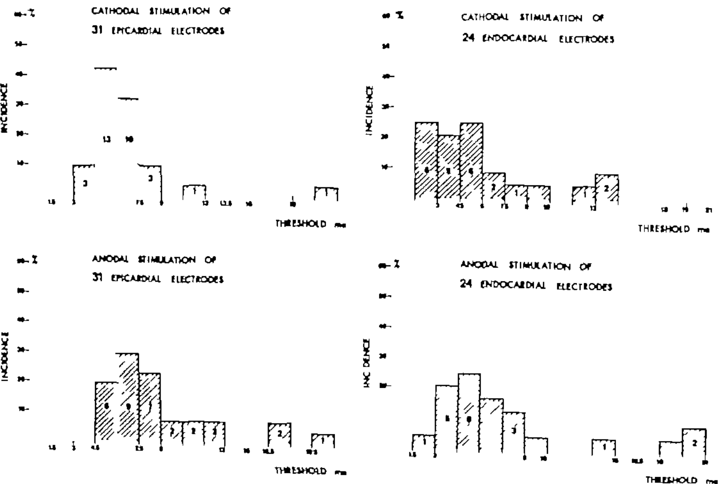


Fig. 1. Histograms of anodal and cathodal thresholds in chronically implanted epicardial and endocardial pacemaker electrodes.

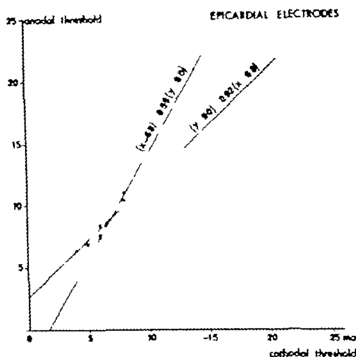


Fig. 2 Anodal versus cathodal thresholds in 31 chronically implanted epicardial electrodes.

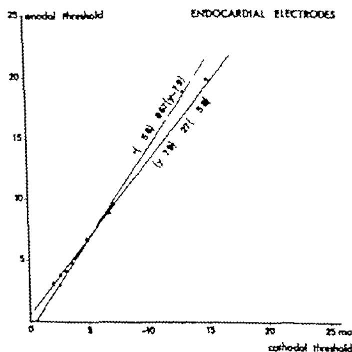


Fig. 3. Anodal versus cathodal thresholds in 24 chronically implanted endocardial electrodes.

The results of Harris and colleagues[24] and of Davies and Sowton[25] are in agreement with our findings in that epicardial electrodes were found to have a higher threshold than endocardial electrodes However the reported differences were much greater 4 to 4.9 versus 22 to 25 microjoules, respectively If these results would have been expressed in terms of current this is equivalent to a ratio of approximately 1 2 The late thresholds however were obtained only several weeks or months after implantation[25] whereas our measurements were all finished at least 11 months after implantation A gradual increase in endocardial thresholds during a longer follow-up should be considered as a possible explanation of our differing results, as well as differences in electrode design and technique In a previous study[26] it was found that threshold values of chronically implanted epicardial electrodes differed only approximately 15 per cent for anodal and cathodal stimuli It is still commonly held that the ratios of cathodal and anodal thresholds are much lower [illegible] Davies and Sowton[25] found a ratio of 1 16 expressed in microjoules which is equivalent to approximately 1 4 in terms of current thresholds Hoffman and Cranefield[30] mention a ratio of 1 2 or 1.3 between cathodal and anodal thresholds. Our previous measurements[1,26] were done through epicardial electrodes connected by transcutaneous wires to an external pacemaker unit. Infection was a frequent problem in those patients. It is of some interest therefore that the results of the present study (Figs. 2 and 3) in a new series of patients with implanted pacemaker units and without a single instance of infection[32] confirm our previous findings.

With epicardial electrodes, the mean values for cathodal and anodal threshold are 6 8 and 9 0 Ma. respectively A similar ratio is obtained when the mean thresholds for cathodal and anodal stimulation of endocardial electrodes are compared 5 8 and 7 9 Ma The regression lines give the best estimate of cathodal threshold for each given anodal threshold and vice versa

During the implantation of the electrodes we commonly observed ratios of 1.4 It is assumed therefore that the discrepancies of our results with those in the literature are due to our longer observation period This would mean that—with time—cathodal thresholds rise relatively more than anodal thresholds.

As previously described[1,26] in a few instances the cathodal threshold of an electrode may even exceed its anodal threshold In this series of patients, this paradoxical threshold behavior was again observed. A cathodal threshold of 10.0 Ma. and an anodal threshold of 6.8 Ma. were observed (Fig 3) 17 months after implantation of an endocardial electrode in a 70-year-old woman. After careful examination had shown that these values were correct the endocardial electrode was connected to the anode.

The ranges of the thresholds as shown in Fig 1 would seem to hold some useful information for those who design pacemakers. Even with endocardial electrodes the threshold often reaches values beyond the output power of several commercially available pacemaker units. We doubt the wisdom of the advice to reduce the number of pacemaker batteries[31] when intracardial electrodes are used These pacemaker units should be able to deliver at least 15 Ma into a 500 ohm load on primary implantation In special cases, it will be found necessary to make available much stronger units. In one patient not included in this series, we successfully used a specially designed unit with a 30 Ma. output.

Summary

Thresholds of 31 epicardial and 24 endocardial pacemaker electrodes were measured 11 to 21 months after implantation. It was found that endocardial electrodes had only a slightly lower threshold than epicardial electrodes. When both types of electrodes are chronically implanted differences between cathodal and anodal thresholds were also small It is concluded that pacemaker units used with both types of electrodes should at least have an output of 15 Ma. into a 500 ohm load in order to avoid failure from high threshold

W[illegible] are grateful t[illegible] Prof Dr D Durrer for h[illegible] valuable support [illegible]nd helpful criticism, t[illegible] Dr J

*Vitatron, Dieren, Holland. Type MIP-D6

Strackee for his adv on tatist al nd physical aspects, and to M J Bosveld for his tech ical assistance.

REFERENCES

1 Meijne, N G., Dekker E., va Erven, F A Mellink, H. M and Harff E. G Algemene chirurgische aspecten van pacemakerimplantaties, Nederl. T Geneesk. 111 1191 1967
2. Elmqvist, R., Landegren, J Petterson, S. O Senning, A and William-Olsson, G Artificial pacemaker for treatment of Adams-Stokes syndrome and slow heart rate, Am. Heart J 65 731 1963.
3. Dekker E., Büller J and Schuilenburg R. M Aids to electrical diagnosis of pacemaker failure, Am. Heart J 70 739 1965
4 Dekker E Büller J and van Erven, F A. Unipolar and bipolar stim lation thresholds of the human myocardium with chronically im planted pacemaker electrodes, Am Heart J 71:671 1966.
5. Lagergren, H and Johansson, L. Intracardiac stimulation for complet heart block, Acta chir Scandinav 125:562, 1963
6. Wilcoxon, F Individual comparisons by ranking methods, Biometrics Bull. 1:80 1945
7 Mann, H B and Whitney D R. On test of hether one of two random variables is stochastically larger tha the other A M th. Statistics 18:50, 1947
8. Dierel, P B and Friese, G. Zum Thema der langfristigen elektrischen Reizung des Herzens Die gewöhlichen Veränderungen in der Umgebung der Herzmuskelelektrode, Z. Kreislaufforsch. 52:1 1963.
9 Noeske, K and Knothe, W Pathologisch-anatomische Veränderungen im Bett von Schrittmacherelektroden, Thoraxchirurgie 13:273 1965
10. Parsonnet, V Zucker I R Kannerstein, M L., Gilbert, L., and Alvares, J F The fat of permanent intracardiac electrodes, J Surg Res 6:285 1966
11. Zoll, P M nd Linenthal, A External and internal electric cardiac pacemakers, Circulation 28:455 1963
12. Preston, T A Judge, R D Lucchesi, B R and Bowers, D L Myocardial threshold in patients ith artificial pacemakers, Am J Cardiol. 18:83 1966
13 Thalen H. J Th., and Berg, Jw van den Threshold measurements and electrodes of the cardiac pacemaker Acta Physiol Pharmacol Neerl. 14:227 1966.
14. Ji on, G. G., Marchand, P Milner M and Obel, W P A long-term study of threshold values and output characteristics of cardiac pacemakers, Thorax 22:63 1967
15 Weitl, J J Fontaine, G., and Facquet, J Le seuil d'entraînement électrosystolique chez l'homme et ses variations dans le temps, Arch. mal. Coeur 60:605 1967
16 Lagergren, H Dahlgren, S., and Nordenstam H. Cardiovascular tissue response to intracardiac pacemaking Acta chir Scandinav 132:696, 1966.
17 Schneider H. Physical principles of artificial stim lation of the heart. Stimulation of the canine heart in situ, Am. Heart J 6 :628, 1963
18 Briller S.A., Gesselowitz, D B., Arlinger S. D Danielson, G K., Jaron, D and Joyner C. R. The electrical interaction between artificial pacemakers and patients, with pplications t lectrocardiography Am Heart J 71:656 1966.
19 Greatbatch, W The electrode interface between man and a prosthetic stim lator I E E E. I ter Conv Rec 9 109 1967
20 Albert, H. M Glass, B A., P tman, B and Robichaux, P Cardiac timulation threshold h onic study Ann. New York Acad Sc. 111:889 1964
21 Furman, S., Denize A., Escher J W and Schwedel, J B Energy consumption for cardiac timulation as function of pulse duration, J Surg Res. 6:441 1964.
22 Nash, D T Threshold of cardiac stimulation acute studies, Ann. New York Acad Sc. 111:877 1964.
23 Sklar H Escher D J W Furman, S., and Sch edel J B The energy threshold for right ventricular endocardial stimulation as function of pulse duration, Clin. Res 13:220, 1965
24 Harris, A Bluestone, R Busb E., Davies, G Leatham, A., Siddons H and Sowton, E The management of heart block, Brit Heart J 27:469 1965
25 Davies, J G and Sowton, E Electrical threshold of the human heart, Brit Heart J 28:231 1966.
26. van Erven F A Het complete atrioventriculaire block bij de mens en de behandeling daar van met electrische stimulatoren, De Bilt, 1965 Cuperus, p 131
27 Brooks, C. McC. Hoffman, B. F Suckling E. E and Orias O Excitability of the heart, New York 1955 Grune & Stratton, Inc p 86
28 Brockman, S K Webb, R C and Bahnson, H T Monopolar entricular stimulation for the control of acute surgically produced heart block, Surgery 44:910, 1958.
29 Dam, R. Th van, Durrer D Strackee, J and T eel, L H van der The excitability cycle of the dog left ventricle determined by anodal, cathodal and bipolar tim lation Circulation Res. 4 196, 1956.
30. Hoffman, B F and Cranefield, P F Electrophysiology of the heart, New York, 1960, M Graw Hill Book Company Inc., p 220
31 Race, D Stirling G R Emery P and Bremner J Electrical stimulation of the heart, Ann. Surg 158 100, 1963.
32. Lister J W Esher D J W Furman, S. Sch edel, J B Stein, E., and Damato, A. M Heart block A method for rapid determination of causes of pacing failure in artificial pacemaker systems, Am. J Cardiol 18:64, 1966.
33 Meijne, N G Mellink, H. M Dekker E. and Erven, F A van Experiences in pacemaker implantation, J Cardiovas. Surg 8:121 1967
34 Lagergren, H Permanent intracardiac stimulation for complete heart block and Adams-Stokes syndrome. Progress and clinical experience, Acta chir Scandinav 132:663, 1966

Direct read-out of cardiac output by means of the fiberoptic indicator dilution method

*Paul G. Hugenholtz, M.D.**
*Henry R. Wagner, M.D.***
*Walter J. Gamble, M.D.****
*Michael L. Polanyi*****
Boston, Mass.

Ever since the introduction by Stuart and Hamilton of the dye dilution principle for the determination of cardiac output, investigators have searched for a simplification of this procedure with the ultimate aim of providing a virtually instantaneous read-out of this physiologic variable.

Difficulties with conventional dye dilution sampling systems, employing catheters and an extracorporeal cuvette as the sampling site, have necessitated a variety of improvements, including devices correcting for artifacts and for early recirculating indicator. Even with these adaptations, which usually require some further calculation for the assessment of the primary indicator dilution curve, the need for withdrawal of blood has not been obviated. This study presents a clinical evaluation of a method, the principles of which have been described by our group in previous publications.[1-4] The essential improvements employed in this study are the inclusion of a simple integrating circuit, a direct read-out meter, and a device permitting the calibration of the system at the onset of cardiac catheterization. This new calibration system requires no more than 3 ml. of arterial blood and permits a rapid execution of the calibration procedure and obviates all needs for further calculations.

The method to be described was based on the observation that concentrations of indocyanine green dye sampled by the fiberoptic catheter (FO) in the central aorta after injection of the dye into the left ventricle or into the right side of the heart usually fell to less than 1 per cent of the peak concentration before recirculation was detected, a circumstance also observed with other indicator dilution systems.[4] The explanation for this observation appears to be the absence of any mixing in the sampling system be-

Supported in part by Program Project Grant HE-10436-01 and Traineeship Grant HE-5310-08 from the National Institutes of Health, Bethesda, Md.
This work was done during the tenure of an Established Investigatorship of the American Heart Association.
Received for publication May 6, 1968.
*Senior Associate in Cardiology, Children's Hospital Medical Center; Assistant Professor of Pediatrics, Harvard Medical School, Boston, Mass.
**Fellow in Medicine (Cardiology), Children's Hospital Medical Center; Research Fellow in Pediatrics, Harvard Medical School, Boston, Mass.
***Associate in Cardiology, Children's Hospital Medical Center; Associate in Pediatrics, Harvard Medical School, Boston, Mass.
****Research Scientist, American Optical Company, Framingham, Mass.

February 1969 Vol. 77 No. 2 pp. 178-1??

tween dye particles in the primary circulation and in the first recirculation. In fact such mixing in the conventional catheter cuvette sampling systems may be the reason for the usual superimposition of diminishing amounts of indicator of the first circulation with increasing quantities of indicator of the recirculation. Since there is virtually no delay in the present sampling system this separation of the two appearances of indicator permits the direct integration of the indicator concentration of the primary circulation without the need to correct for recirculation. Should early recirculation be present for any reason such as unsuspected left-to-right shunting a sophisticated cardiac output computer such as presently available, would have to be used instead of the simple integrator.

Methods and materials

In 15 individuals with congenital heart disease 150 cardiac output studies were carried out. In addition 3 healthy dogs were studied with multiple injections proximally and distally in the circulatory system. These studies formed a part of a complete cardiac evaluation prior to surgery and included right and left heart catheterizations.

All patients were premedicated with a mixture of meperidine (25 mg. per milliliter), Phenergan (12.5 mg. per milliliter) and Thorazine (12.5 mg. per milliliter) in a dosage of 1 ml. per 30 pounds with a maximum of 2 ml. All studies were done in the supine position. Most of the patients were asleep at least part of the study; however, in 5 individuals, a variety of interventions, such as Isuprel infusion

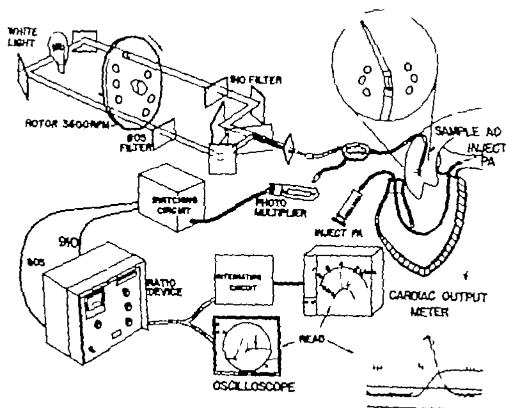


Fig. 1. Schematic showing the principles of the fiberoptic hemoreflection system. White light (left upper hand corner) is changed into rapidly alternating pulses of monochromatic light at 910 and 805 mm. wave lengths. These pulses enter the fiberoptic catheter through efferent fibers and emerge in the arterial system. After their return through afferent fibers the reflected light intensities are measured on a photomultiplier. The ratio of the reflected light intensities is instantaneously computed and passed to an integrating circuit. Its output and the original curve are both recorded on a photographic recorder and displayed on an oscilloscope. The output also may be read off directly from the cardiac output meters (see Fig. 3).

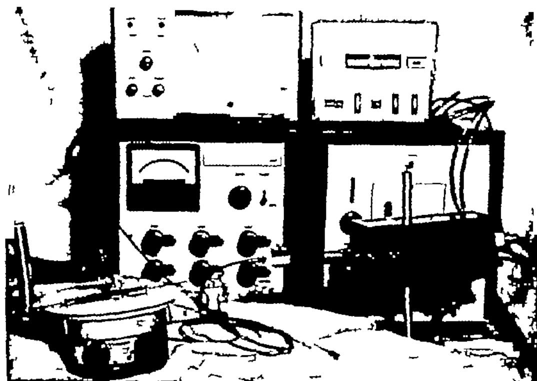


Fig. 2. Components utilized in the present system. Left upper hand corner: integrating circuit and cardiac output meter (see Fig. 3). Right upper hand corner: cardiotachometer. Left middle: fiberoptic hemoreflector (electronic assembly). Right middle: fiberoptic hemoreflector (optical assembly). Left lower hand corner: magnetic stirrer (Fisher Scientific) stainless steel holder. No. 6 fiberoptic catheter. Hamilton syringe. Right lower hand corner: separate photomultiplier assembly with fiberoptic and high voltage cabling.

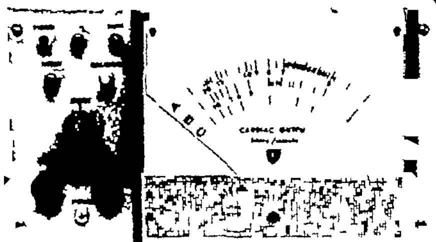


Fig. 3. Cardiac output meter. The panel on the left hand side contains the control knobs for balancing of the circuit, the "hold" or "run" positions and indicator light, power switch and a gain control. The letter potentiometer permitted selection of three ranges, A for cardiac outputs varying from 4 to 30 L. per minute, B for a range of 15 to 2 L. per minute and C for 7.5 to 1 L. per minute. Selection of the proper range has to be made at the onset of the study. Adjustment in the gain control may be made between curves if the readings were to exceed the range.

intracardiac pacing or exercise was employed. This led to a change in the hemodynamic state and permitted the study of cardiac output at different levels of cardiac activity.

Details regarding the in vivo fiberoptic hemoreflection system have been given in an earlier study.[3] The apparatus and components used were constructed by the American Optical Company, Southbridge, Mass. A schematic review of the apparatus appears in Fig. 1. An illustration of the apparatus utilized and of the cardiac output meter is given in Figs. 2 and 3.

A modification of the original description of the in vivo hemoreflection system was employed in the last five patients studied. It consisted of a separate photomultiplier assembly measuring 3 by 3 by 5 inches, attachable to the Schonander Koordinat table and connected to the rest of the instrumentation by a 15 foot flexible fiberoptic extension cable (Fig. 2). This modification made the entire assembly much more mobile than the original one. It will permit rack-mounting of the remaining equipment, facilitating the use of the fiberoptic apparatus during cardiac catheterization.

The components necessary for the calibration procedure are shown in Fig. 2. They consist of a sterilizable, 5 inch nylon disc in the center of which a 5 ml. glass cuvette, containing a ½ inch long Teflon coated magnetic stirrer is placed. The entire assembly may be autoclaved and attaches by adjustable screws to a Fisher Scientific model 14-511 ? magnetic stirring device. A stainless steel adjustable arm with a clamp permits the placement of the fiberoptic catheter tip inside the cuvette. Three milliliters of arterial blood fills the cuvette to approximately 3 mm. above the fiberoptic sensing tip. The stirrer is set to rotate at about 350 revolutions per minute. A 50 μL. Hamilton micropipette completes the equipment. The latter requires gas sterilization. All components with the exception of the stirring apparatus may be assembled by the operator at the outset of or prior to the procedure.

Calibration of the system was made in two steps. First, with no dye in the 3 c.c. blood sample, the meter was set to zero with the position control. Next, 20 μL. of a mixture of cardiogreen containing approximately 5 mg. of the indocyanine green per milliliter of diluent was added to the 3 c.c. of the blood sample. With this mixture added to the blood, the meter was set to half scale with the span control. This reading as well as the control value were in each case recorded on a photographic recorder, model No. 550 Sanborn Hewlett Packard. The dye mixture added to the sample was the same as that used for injection into the patient. With the instruments so calibrated, full scale deflection on the meter corresponds to a concentration of approximately 55 mg. of indocyanine green per liter of blood. This two-point calibration was considered adequate on the basis of previous in vitro calibration results[4] showing a virtual linear calibration curve for doses of indocyanine green as high as 50 mg. per liter of blood, and an unchanged calibration with desaturation or when the hematocrits varied from 30 to 55 per cent. An example of such a calibration curve is shown in Fig. 4.

In all other respects, the calibration

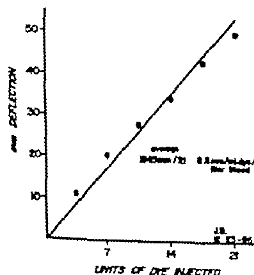


Fig. 4. Calibration deflection obtained on an eleven-year-old boy with chronic anemia and hemosiderosis (hemoglobin 6 Gm., hematocrit 30 per cent). A linear response is observed with doses as high as 20 units or 123 mg. of dye per liter of blood. (1 unit = 2.2 mm. per milliliter of dye per liter of blood. 1 ml. dye mixture contains 5.95 mg. of indocyanine green.)

procedure corresponded to that described in previous studies utilizing the formula given below

$$\text{Cardiac output liters per minute} = \frac{60 \times \text{cal defl} \times \text{vol dye injected}}{\text{Curve area}}$$

Calibration deflection = The average deflection from the base line per milliliter dye added to 1 ml of blood (mm./ml dye/L. blood)

Volume dye injected = The volume of indocyanine green mixture injected into the patient at the time of the dye curve (ml dye)

Curve area = The planimetrically obtained

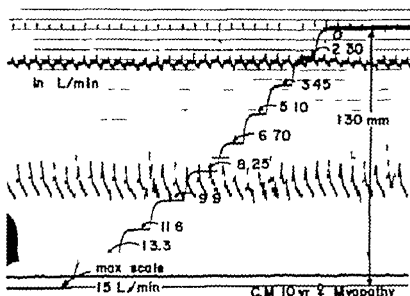


Fig 5 Example of integrator calibration (scale B) Values of cardiac output falling between the measurements have to be derived by interpolation (see Fig 3).

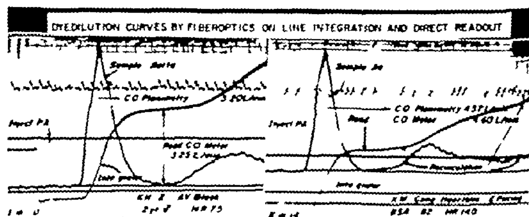


Fig 6 Representative curves in a twelve-year-old boy with congenital heart block before and after intracardiac pacing Sampling was carried out in the aorta Injection into the pulmonary artery performed The integrator output is read from the cardiac output meter at the precise moment (indicated by vertical arrow) where the primary curve (on the monitoring oscilloscope) *returns to the base line and reaches its lowest point.* At this moment, the integrator output does not show further increments indicating that integration of the primary curve has virtually ended. This reading could be obtained regardless of the degree of tachycardia.

area of the inscribed curve (mm deflection × seconds)

60 = seconds per minute

The cardiogreen mixture utilized throughout the study was made by mixing 20 ml of distilled water and 1 c.c. of human albumen in 125 mg of cardiogreen powder Previous experience has shown that the addition of albumen stabilizes the mixture for over a 4 hour period the time usually necessary for complete cardiac catheterization. The cardiogreen was injected into the patient in amounts of 1 ml for each curve in a variety of locations inside the heart. Injection was carried out either by hand employing a volumetric pipette and 5 ml. of saline as flush or by a Cordis power injector as a mixture of 1 ml of the dye in 4 ml. of saline In the latter instance, the catheter remained connected to the injecting syringe throughout the study period assuring delivery of virtually the same amounts of indicator Since the injecting pressure varied and different lengths of catheter were used, the exact volume delivered during the injections was verified after completion of the study by means of volumetric measurements.

The integrating circuit required electrical calibration only The circuit was first balanced in the hold position with zero adjust control and after immersion of the fiberoptic tip in undyed blood adjustment for drift was made in the run position with the offset control until the needle remained stationary at any position on the scale (Fig 3) By means of a calibrating signal source giving a series of readings on the meter between zero and 30 L. per minute and a series of deflections from the base line on the photographic recorder subsequent readings on the meter made during the procedures could be compared with deflections recorded on the paper during the curves (Fig 5) This was usually carried out before the fiberoptic catheter was inserted in the cuvette. Both steps required at most, a 10 minute period A further reduction in time may be achieved by balancing the integrator before the start of the procedure.

Three series of data were obtained and a statistical analysis carried out. First, in 124 curves, the direct reading from the meter was obtained by stopping further integration at that instance where by

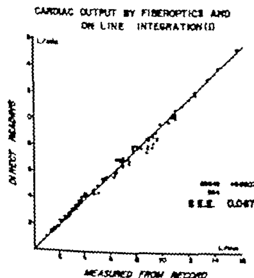


Fig 7 Relationship between the direct reading of cardiac output from the meter and the result obtained subsequently by measuring the integrator output on the photographic record. There was a slight but consistent overestimate of cardiac output by direct reading

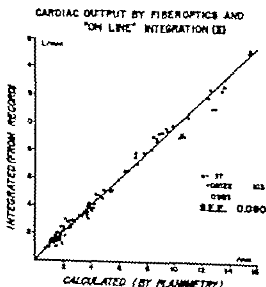


Fig 8 Comparison of the results for cardiac output after measurement of the integrator record and the output calculated in the conventional manner with planimetry of the curve and application of the Stewart Hamilton formula.

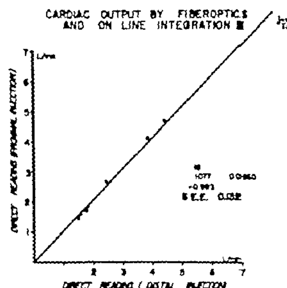


Fig. 9. Relationship between cardiac output determined in quick succession in the same individuals after proximal injection (LV or PA) and distal injection (RA or SVC). The result for the last site of injection is usually a lower reading than after proximal injection (see text).

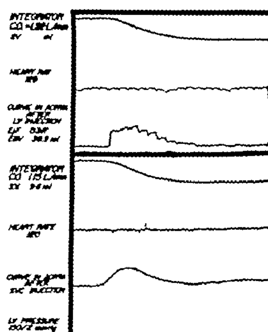


Fig. 10. Examples of cardiac output determination in dog rendered hypovolemic. The results after left ventricular injection are slightly higher than those obtained after superior vena cava injection, which followed immediately afterward. Note how even after distal injection the curve returns to the base line permitting electronic integration before recirculation takes place.

visual inspection of the curve on the oscilloscope upon return to the base line was noted (Fig. 6). The result was compared with the reading obtained from the simultaneously recorded but subsequently measured deflection from the base line of the integrator output at that instant (Fig. 7). Second, in 134 observations, an analysis was carried out of the relationship of this direct reading to the result after conventional calculation of the dye dilution curve employing planimetry and the formula given above (Fig. 8).

Finally, in order to evaluate the effect of injection of indicator further upstream and of sampling further downstream, a series of 19 cardiac output determinations was obtained in quick succession from widely varying points. Only instances where the interval was less than two minutes between the determinations and where heart rates differed less than 10 beats were accepted for this comparison (Fig. 9).

Results

The data concerning the first series of comparisons are given in Fig. . It can readily be seen that over a range of 1 to 16 L. per minute of cardiac output a highly significant linear agreement ($r = 0.994$) existed between the results predicted from the direct reading of the integrator meter and those measured subsequently from the recorded integrator output. However, calculation of the regression equation indicated an overestimate by direct reading of 3.3 per cent (Fig. 7).

Regarding the second correlation, the comparison of the direct integrator output with the conventional calculation of cardiac output by planimetry of the curve, a similar high degree of agreement was found ($r = 0.992$). However, regression analysis again indicated that the results by direct integration overestimate the subsequently measured data. The average overestimate was 4.2 per cent (Fig. 8). Both errors indicate that the "automated" cardiac output may exceed the normally

computed result by an average of 7.3 per cent. The final analysis concerned the comparison of results after injection in the circulatory system at a point distal to those carried out at a point more proximal. Fig. 9 indicates that results after injection at the proximal site invariably exceed those carried out more distally up to a maximum of 13 per cent.

Discussion

The data obtained in this study indicate that cardiac output may be determined under a variety of circumstances, i.e., Isuprel infusion, intracardiac pacing, or exercise, by fully automatic integration of the curve of the indicator concentration presented to the sensor of the fiberoptic system. Thus, cardiac output determination without subsequent calculation and without the need for withdrawal of blood has become feasible. The results also indicate that an overestimation of an average 7.3 per cent occurs when direct readings are compared with those calculated in the standard fashion. This overestimation occurs because of a slightly premature reading of the integrator dial setting and because of incomplete integration of the total area. Compensation for this overestimate by adjustment of the integrator apparatus appears to be a logical solution to this problem. If such correction is made, the remaining error is the inherent variability of the dye dilution principle.

Of more clinical importance is the problem of proximal versus distal injection of indicator (Figs. 9 and 10). As shown in Fig. 10, the indicator dilution curve returns to the base line for a sufficiently long period of time to permit on-line read-out of the integrated record even after distal injection. Yet, in all observations a consistently higher result for stroke volume and cardiac output was seen after proximal injection. This difference appears unlikely to be due to a sampling problem. Rather, the finding seems to correspond to those found by other workers. The explanation given for this observation by Ryan and associates was that the more distal the injection of indicator was carried out, the wider the spread of the indicator concentration became and hence the greater the chance of overlap of the primary circulation with the first recirculation. They found that in the same patients proximal, i.e., left ventricular or pulmonary artery injection under otherwise similar circumstances yielded results which were between 8 or 10 per cent higher than when injections were carried out distally such as in the right atrium or superior vena cava. In other studies from this laboratory, similar observations have been reported.[a] Since in these studies, results after proximal injection showed closer agreement with data for stroke volume derived by the angiocardiographic method, it appears that the distal injection may actually underestimate the true value. On the other hand the possibility that the angiocardiographic method may overestimate stroke volume as a result of injection of the contrast medium is by no means excluded. In the absence of more conclusive information on this subject, a definite adjustment of cardiac output scale to compensate for varying sites of injection is not warranted at this time.

Summary

The feasibility of determining cardiac output by the indicator dilution principle without the need for any calculation or the withdrawal of blood was studied in 15 patients and 3 dogs.

A total of 150 curves were utilized and good agreement found between the "direct" reading obtained from a cardiac output meter and the result derived from more conventional indicator dilution calculations. Cardiac outputs were studied with varying heart rates, samplings, and injection sites, and varied from 1 to 16 L. per minute.

The advantages of the method lie in its speed, the use of a conventional indicator (indocyanine green), the ease of calibration which is accomplished with only 3 ml. of blood, and the absence of the need for repeated withdrawal of arterial blood samples.

REFERENCES

1. Hugenholtz, P. G., Gamble, W. J., Monroe, R. G., and Polanyi, M. L.: The use of fiberoptics in clinical cardiac catheterization. II. In vivo dye-dilution curves, Circulation 31:344, 1965.

2. Wagner H R Gamble, W J Albers, W H and Hugenholtz, P G Fiberoptic dye dilution method for measurement of cardiac output A comparison with the direct Fick and angiocardiographic method, Circulation 37:694 1968.
3. Hugenholtz, P G Wagner H R and Sandler H. The in vivo determination of left ventricular volume A comparison of the fiberoptic-indicator dilution and angiocardiographic method, Circulation 37:489 1968
4. Holt, J P Indicator-dilution methods Indicators, injection, sampling and mixing problems in measurement of ventricular volume, Am J Cardiol 18:208, 1966.
5. Polanyi, M L., and Hehir R In vivo oximeter with fast dynamic response, Rev Scient. Inst. 33 1050 1962.
6. Ryan T J Williams, J H and Abelmann, W H. Influence of injection site upon observed flow relationship between right and left ventricle, Abstract presented at 34th Scientific Session of American Heart Association, *Circulation 24* 1028 1961

The second heart sound in coronary artery disease
A phonocardiographic assessment

Walter H Caulfield Jr Captain MC USAR
Roger H Smith Major MC USA
Robert B Franklin Colonel MC USA
San Francisco Calif

Ever since attention has been focused on variations in the second heart sounds and their significance by Leatham[1] and Gray cardiologists have continued to gain important information concerning cardiovascular dynamics by scrutinizing the second sound Recently attention has been directed to the presence of paradoxical splitting of the second sound in coronary artery disease.[3] Early reports mentioned that the paradoxical splitting was present only during or for a few days after an episode of acute myocardial ischemia. A subsequent article reported the presence of this abnormality in approximately one third of patients with cineangiographically documented coronary artery disease and another stressed its importance in the diagnosis of occult myocardial infarction. A recent article presented phonocardiographic evidence of paradoxical splitting in selected patients.

However the frequency of paradoxical splitting in patients with coronary artery disease has not been documented by phonocardiography to the authors knowledge This is particularly important since paradoxical splitting can be confused with the diminution of heart sounds that occurs with inspiration Furthermore, until the frequency of this finding is ascertained its value in the diagnosis of coronary artery disease remains unknown.

Methods

Twenty consecutive patients treated on the wards and clinics at Letterman General Hospital who had unequivocal documented myocardial infarctions by history laboratory studies, and electrocardiographic findings were studied at least four weeks after an acute myocardial infarction. Due to the nature of the illness, no patient was studied during the acute phase of an infarction. Patients with lesions known to cause paradoxical splitting such as left bundle branch block, severe aortic stenosis, left ventricular overload (patent ductus arteriosus with large left-to-right shunt) Wolff Parkinson White syndrome and severe hypertension were excluded. Congestive heart failure (CHF) in this study was defined as the presence of paroxysmal nocturnal dyspnea orthopnea or

From the Division of Cardiology Department of Medicine, Letterman General Hospital and the United States Army Medical Research Unit, Presidio of San Francisco, San Francisco, Calif 94129

This material has been reviewed by the Office of the Surgeon General, Department of the Army and there is no objection to its presentation and/or publication. This review does not imply any endorsement of the opinions advanced or any recommendation of such products as may be needed

Received for publication May 1 1968

peripheral edema responsive to digitalis and diuretic therapy Angina pectoris was considered present only when manifested in its classical form [8]

Auscultation was performed in all twenty patients by at least two investigators with specific emphasis on the second heart sound throughout the respiratory cycle. Prior to phonocardiography the examiners recorded the results of their examination Physiological or normal splitting was considered present when splitting increased in duration during inspiration paradoxical splitting when the second sound was single in inspiration and split in expiration, the reverse of normal

Phonocardiography was performed with a direct contact microphone (Sanborn Co Waltham Mass. No 350-1700-B-C10) between the frequencies of 100 to 400 cycles per second Sound recordings were taken routinely from the right and left second intercostal spaces and the fourth left intercostal space at the sternal border. Additinoal recordings were taken from other areas, particularly the third left intercostal space when appropriate. Recordings were made continuously through-

Fig. 1. *A* Phonocardiograph of patient No. J. Although one component of the second sound (S_2) is present during inspiration and two during expiration only one component occurs before the dicrotic notch. This must, therefore be 1 (and S_2 is, therefore physiologically split). *B* Phonocardiograph of a patient with left bundle branch block and paradoxical splitting of S_2. Note that both components of S_2 occur before the *DN*.

Table I Summary of data

Case No.	Age	Sex	History		Infarct			Second heart sound	
			Angina	CHF	Age at occurrence	Location (ECG)	Medication	Auscultation	Phonocardiogram
1 T S	60	M	Yes	Yes	46, 56	Inferior anterior	Pronestyl	Physiol. split	Physiol. split
2. A M	19	M	Yes	Yes	49	Inferior anteroseptal	Digoxin q nidine	Physiol. split	Physiol. split
3. D R	41	M	Yes	Yes	37	Anterior	Peritrate	Physiol. split	Physiol. split
4 C I	59	M	Yes	N	55	Anteroseptal	Peritrate	Physiol. split	Physiol. split
5 R D	47	M	Yes	Yes	4	Anteroseptal	Digoxin, Peritrate	Single	Physiol. split
6. W B	61	M	N	N	59	Anterior inferior	None	Physiol. split	Physiol. split
7 J A	65	M	Yes	Yes	65	Inferior	Digoxin quinidine	Physiol. split	Physiol. split
8 A B	49	M	N	Yes	49	Anterior	Digoxin	Physiol. split	Physiol. split
9 J A	70	M	Yes	Yes	67 70	Inferior anterior	Digoxin	Physiol. split	Physiol. split
10 A C	72	M	No	N	62	Inferior	None	Single	Physiol. split
11 J I	33	M	Yes	Yes	43 46	Anteroseptal	Digoxin Lersa t n	Single	Physiol. split
12. Z O	57	M	Yes	N	47	Anteroseptal	None	Physiol. split	Physiol. split
13 B B	52	M	Yes	N	48 51	Inferior anteroseptal	None	Slngle	Physiol. split
14 S D	38	M	Yes	Yes	38	Inferior	None	Physiol. split	Physiol. split
15 O S	49	M	N	N	49	Inferior	None	Physiol. split	Physiol. split
16. W F	47	M	N	Yes	47	Posterior	Digoxin	Physiol. split	Physiol. split
17 J T	43	M	N	N	43	Anteroseptal	None	Physiol. split	Physiol. split
18 N J	72	F	Yes	N	64	Anteroseptal	None	Paradox. split	Physiol. split
19 L I	55	M	Yes	Yes	53	Inferior	Iso rd l	Physiol. split	Physiol. split
20. C I	59	M	Yes	Yes	59	Inferior anteroseptal	Digoxin	Physiol. split	Physiol. split

out multiple respiratory cycles while the patient was breathing normally in the supine position.

The second heart sound and its two major components representing aortic (A) and pulmonic (P_2) valve closure were identified by their relation to the indirect carotid pulse recorded through a piezo-electric device (Sanborn 3/4 Pulse Wave Attachment) The dicrotic notch of the indirect carotid pulse tracing occurs 0 01 to 0.04 second after the aortic component of the second sound is recorded on the phonocardiogram Normally I occurs after A_2 In paradoxical splitting since I_2 precedes A both components must occur before the dicrotic notch

Lead II of the electrocardiogram and a pneumogram were also recorded simultaneously for time reference All recordings were made on an optical recorder (Electronics for Medicine DR 8 White Plains, N Y) at 50 or 75 mm per second paper speed

Results

The results are tabulated in Table I Nineteen of the twenty patients were male The average age was 54 9 years. The patients ages at the time of the first infarction averaged 51 1 years Fourteen patients (70 per cent) had angina pectoris and twelve (60 per cent) had experienced or were being treated for congestive heart failure Six patients had experienced more than one infarct Of a total of 26 infarcts electrocardiographic localization revealed 11 (4 per cent) to be inferior 9 (36 per cent) anteroseptal 5 (1 per cent) anterior and one (4 per cent) posterior

On auscultation fifteen patients were noted to have physiological splitting of the second sound and this was confirmed by phonocardiograms. Four patients were thought to have a single sound but phonocardiography revealed normal close splitting One patient (N J) was thought by all the investigators to have paradoxical splitting Phonocardiography (Fig. 1) indeed showed that a single component of the S_2 was present during inspiration and two components during expiration However when the sounds were related to the dicrotic notch of the indirect carotid pulse tracing only one component of S_2 occurred before the dicrotic notch. Therefore physiological splitting was present. A_2 was inaudible during inspiration, giving the auscultator the false impression of the presence of paradoxical splitting. Therefore all twenty patients had physiological splitting of the second heart sound.

Discussion

Analysis of the second heart sound (S_2) by auscultation results in subjective information concerning the relationship between aortic (A_2) and pulmonic (P) valve closure It is inferred that paradoxical splitting is present if one component of S_2 is heard during inspiration and two components during expiration. However, to show that there are two components of S_2 present during expiration and one during inspiration is inconclusive. It is their relationship to the dicrotic notch of the indirect carotid pulse tracing which occurs 0 01 to 0 04 second after aortic valve closure that is the definitive objective parameter It is only when both components of S_2 occur before the dicrotic notch that paradoxical splitting is present. This was well illustrated by Patient N J (see preceding)

In paradoxical splitting of S_2, all that can be deduced is that I precedes A_2, which is a reversal of the normal. This may be due either to a prolonged left ventricular ejection period (mechanical) or to delayed onset of left ventricular contraction (electrical) It has recently been suggested that asynergy of left ventricular contraction occurs in coronary artery disease.[4] This may result in a mechanical delay of A causing paradoxical splitting However it may be that A_2 is faint following acute myocardial ischemia giving the false impression of reversed splitting

Our study fails to confirm an appreciable incidence of paradoxical splitting in an unselected group of patients with coronary artery disease who survived the acute phase of myocardial infarction We agree with others that it is difficult to study patients who are acutely ill and we did not attempt to do so. Therefore the incidence of paradoxical splitting may well be higher in patients during an acute

ischemic episode or in those suffering from a more severe form of the disease who need further evaluation. However in unselected patients with coronary artery disease who are not suffering an acute episode its incidence is low zero in our series.

Therefore, although paradoxical splitting may be a useful auscultatory accompaniment of acute myocardial ischemia it does not appear to be a frequent finding in an unselected group of patients with coronary artery disease who have survived an infarction.

Summary

The second heart sound (S_2) was assessed clinically and by phonocardiography in twenty patients with coronary artery disease. Phonocardiography revealed normal splitting in all twenty and illustrated the need for a reference (indirect carotid pulse) in the assessment of S_2.

The authors thank M Jor Homer Lillie, MC USA, M Irving F Mikanea, SFC Ed ard R. Rice and Mrs. Norma Schmidt for id in taking the phonocardiograms, and Miss Linda Brennan for preparation of the manuscript.

REFERENCES

1 Leatham A. Splitting of the first and second heart sounds, Lancet 2:607 1954.
2 Gray I R. Paradoxical splitting of the second heart sound Brit. Heart J 18:21 1956.
3 Yurchak, P M and Gorlin, R Paradoxical splitting of the second heart sound in coronary heart disease, New England J Med. 269 741 1963
4. Bloomfield, K. K. Clinical evaluation of heart. V Paradoxical splitting of second sound, Ohio State M J 59:61 1963
5. Cohen, L. S Elliott, W C., Klein, M D and Gorlin, R. Coronary heart disease. Clinical, cinearteriographic and metabolic correlations, Am. J Cardiol. 17 153, 1966.
6 Dickerson, R. B., and Nelson, W P Paradoxical splitting of the second heart sound An informative clinical notation, Am. Heart J 67:410, 1964.
7 Agnew T Bucher H M Donald, L., and Seymour J Delayed closure of the aortic valve in ischaemic heart disease, Brit. Heart J 29 775 1967
8 Hurst, J W and Logue, R. B The heart, New York, 1966, McGraw Hill Book Company Inc Ch. 32, p 671

The effect of propranolol (Inderal) on the electrocardiogram of normal subjects

Shlomo Stern, M.D.
Shlomo Eisenberg, M.D.
Jerusalem, Israel

Since the introduction of the β adrenergic receptor blocking agent propranolol into clinical use[1] its efficiency as an antiarrhythmic drug has been clearly demonstrated. More recently it has been used in many other common diseases, such as hypertension and coronary artery disease.[7] In spite of the impressive amount of data published on propranolol, the effect of this drug on the electrocardiogram (ECG) of normal individuals has not yet been established. In the following study we investigated changes in the ECG after administration of propranolol in patients with *no* cardiovascular abnormalities and a normal a priori ECG. The results are described below.

Material and method

In this study we included 21 patients hospitalized in our medical department because of diseases other than cardiovascular or pulmonary. All patients were in good general condition, were without electrolyte or metabolic disturbances and had normal ECG's. Fifteen patients were between 18 and 40 years of age, four were above 40 years, and two were between 16 and 18 years. The tests were performed during the morning hours in the following way: a control 12 lead ECG was taken with a Sanborn 100 direct writing electrocardiograph. Immediately thereafter propranolol was injected intravenously in a dose of 10 mg. diluted in 100 ml. of 5 per cent glucose and was given over a period of 10 to 12 minutes. At the end of the infusion another 12 lead ECG was performed. No side effects were observed during or after the administration of the drug in any of the patients.

The ECG tracings were analyzed for the following data: heart rate, shape, duration, and height of the P wave, P-R interval, amplitude of the Q, R, and S waves in the different leads, the width of the QRS complex, the electrical axis, the S-T segment, the height and duration of the T wave, the Q-T interval and this value corrected for the heart rate ($Q\text{-}T/\sqrt{RR}$, Bazett formula).

Results

When the data from the ECG were analyzed, changes were observed in the following: heart rate, P-R interval, Q-T interval, and the height of the T wave. These changes are summarized in Table I, and illustrative tracings are given in Figs. 1 and 2. It can be seen that all patients exhibited decrease in the heart rate from an average of 76.2 per minute to an average

From the Cardiovascular Unit and Department of Internal Medicine B, Hadassah University Hospital and Hebrew University–Hadassah Medical School, Jerusalem, Israel.
Received for publication May 1, 1968.

Table I Summary of changes in heart rate, P-R interval, Q-T, Q-Tc, and T wave following propranolol

Patient No.	Heart rate (min)		P-R (sec.)		Q-T (sec.)		$Q\text{-}T/\sqrt{RR}$		T wave
	Control	Post propranolol	Control	Post propranolol	Control	Post propranolol	Control	Post propranolol	Post propranolol
1	83	60	12	16	.32	.34	.39	.34	+ increased height
2	53	48	14	18	.38	.34	.36	.31	+ increased height
3	88	75	14	18	.34	35	41	.39	+ increased height
4	75	55	12	12	40	40	44	.38	− no change
5	53	52	12	12	41	40	.39	.36	+ increased height
6	58	50	13	16	40	38	.39	.34	+ increased height
7	85	76	12	14	.34	34	41	.38	− no change
8	102	65	14	18	.36	36	47	38	+ increased height
9	60	55	16	16	.36	.38	.37	.36	− no change
10	77	65	15	15	.36	.36	41	38	− no change
11	60	53	12	12	.39	40	.39	.38	− no change
12	88	70	14	16	.36	.36	44	.39	+ increased height
13	48	42	16	16	40	41	.36	34	− no change
14	72	60	14	16	.34	.36	.37	36	+ increased height
15	74	56	11	14	.33	35	.37	.34	− no change
16	80	70	12	12	.34	.36	40	.39	− no change
17	92	78	14	17	.30	.32	.38	.37	+ increased height
18	105	72	16	18	.29	.3	.39	35	+ increased height
19	75	65	14	14	.36	.35	40	37	+ increased height
20	76	65	16	16	38	40	43	42	− no change
21	90	75	13	14	.46	.36	44	40	+ increased height
Mean	76.2	62.2	0.136	0.152	0.358	0.364	0.400	0.368	
Range	48–105	42–78	0.11–0.16	0.12–0.18	0.29–0.41	0.32–0.41	0.36–0.47	0.31–0.42	

of 62.2 per minute. The P-R interval became longer in 12 patients, and did not change in 9; the average increase was from 0.136 to 0.152 sec. The Q-T interval increased in 11 patients, decreased in four, and did not change in six. When this value was corrected to the heart rate ($Q\text{-}T/\sqrt{RR}$, Bazett formula), a decrease in 20 patients was observed. An increase in the height of the T wave was observed in 12 patients.

Discussion

Clinically, the antiarrhythmic properties of propranolol are very similar to those of quinidine.[9] Moreover, a synergistic action between the drugs was also demonstrated.[10] In view of these observations we expected that its basic effect on the ECG would be similar to that of quinidine. Quinidine, as is well known, increases heart rate, increases P-R interval, prolongs the duration of the QRS complex, prolongs the Q-T interval, induces deviation in the S-T segment, and increases the duration, inversion, and notching of the T wave.[11] Concerning the heart rate, it has been already established that the action of propranolol differs basically from that of quinidine by inducing bradycardia.[1-4] The results of this study demonstrate that other fundamental effects of the two drugs on the ECG are also different. In contrast to the prolongation of electrical systole of the ventricles induced by quinidine, propranolol in 20 out of the 21 patients studied shortened the duration of the Q-T interval. The other striking effect was an increased height of the T wave occurring in 12 of the patients examined. A similar effect was observed on the T wave by earlier investigators.[12] In spite of the decrease in the heart rate the P-R

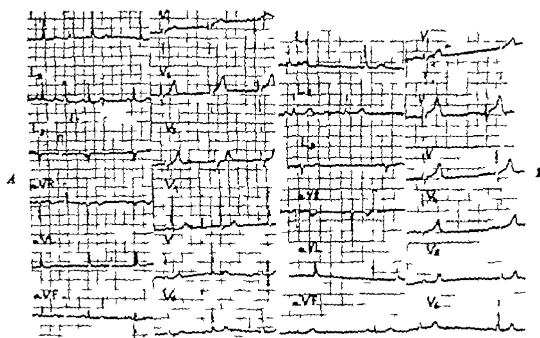


Fig 1 A Control ECG B ECG after propr nolol Note b adycardia, heightened T w ve, and shortened Q-T i terv l

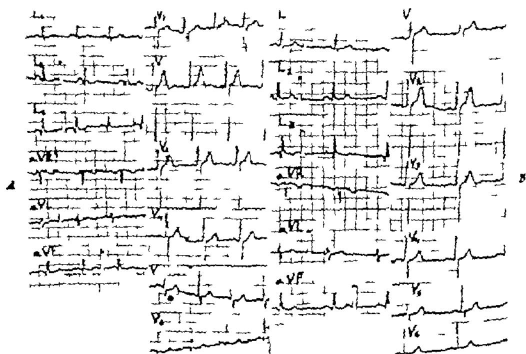


Fig 2 A Control ECG B ECG after propranolol N e bradycardia, heightened T wa and shortened Q-T interval.

interval did not change in nine instances, which was again an effect not seen after the administration of quinidine this latter drug invariably prolongs the atrial conduction time.

In view of the above observations, the synergism between propranolol and quinidine in clinical use and the success with the administration of the two drugs in combination[13-15] may lie in the fact that, although they share the important property of reducing the height and slowing the rise time of the membrane action potential[6] they differ in some other actions. Therefore, each drug may be used in smaller doses, lessening thereby the possible toxic effects but still enhancing the desired antiarrhythmic action

Summary

The effect of propranolol (Inderal) on the ECG of normal individuals was studied in 21 subjects. Over a period of 10 minutes, 10 mg of the drug were administered intravenously An ECG was performed before and immediately after the infusion.

All patients responded with bradycardia. The P R interval increased in 12 patients and did not change in 9 An increase in the height of the T wave was observed in 12 subjects. The Q-T interval did not change in 6 decreased in 4 and increased in 11 The Q-T interval (Bazett formula) became shorter in all but one subject. This effect is opposite to that of quinidine on the Q-T interval.

The above findings are discussed in the light of the described synergistic action of propranolol with quinidine and the successful combination of them in treating various arrhythmias.

REFERENCES

1. Black, J W Crowther A. F Shanks, R. G., Smith, L. H., and Dornhorst A. C A new adrenergic beta-receptor antagonist Lancet 1 1080, 1964.
2. Rowlands, D J Howitt, G and Markman, P Propranolol (Inderal) in disturbances of cardiac rhythm, Brit. M J 1:891 1965
3. Harrison, D C., Griffin, J R., and Fiene T J Effect of beta-adrenergic blockade with propranolol in patients with atrial arrhythmias, New England J Med 273:410, 1965.
4. Schamroth, L. Immediate effects of intravenous propranolol on various cardiac arrhythmias, Am. J Cardiol. 18:438, 1966.
5. Stern, S., and Braun, K. Clinical experience with Inderal (propranolol) in supraventricular arrhythmias and sinus tachycardia, Harefuah 1:371 1966.
6. Prichard, B N C., and Gillam, P M. S. The use of propranolol in the treatment of hypertension, Brit. M J 2 725, 1964.
7. Wolfson, S., Heinle, R. A Herman, M. V Kemp, H G., Sullivan, J M and Gorlin, R Propranolol and angina pectoris, Am J Cardiol 18:345, 1966
8. Grant, R H E., Keelan, P Kernohan, R. J Leonard J C Nockleville, L., and Sinclair K Multicenter trial of propranolol in angina pectoris, Am. J Cardiol. 18:361 1966.
9. Braunwald E An editorial introduction to the Symposium on beta-adrenergic receptor blockade, Am. J Cardiol. 18:303, 1966.
10. Stern, S. Synergistic action of propranolol with quinidine, Am Heart J 72:569 1966.
11. Goodman, L. S and Gilman, A. The pharmacological basis of therapeutics, New York, 1956, The Macmillan Company p. 713
12. Nordenfelt, O Orthostatic ECG changes and the adrenergic beta-receptor blocking agent, propranolol (Inderal) Acta med. scandinav 178:393 1965
13. Stern, S. Conversion of chronic atrial fibrillation to sinus rhythm with combined propranolol and quinidine treatment, Am Heart J 74 170, 1967
14. Stern, S., and Borman J. B. Early conversion of atrial fibrillation after open-heart surgery by combined propranolol and quinidine treatment. Israel J M Sc. In press
15. Reynolds, E. W J and VanderArk, C. R. Treatment of quinidine resistant arrhythmias with the combined use of quinidine and propranolol, Circulation 36:221 1967 (abstr)
16. Vaughan Williams, E. M Mode of action of beta receptor antagonists on cardiac muscle, Am. J Cardiol. 18:399 1966

Abnormal mitral valve motion as demonstrated by the ultrasound technique in apparent pure mitral insufficiency

William L. Winters, Jr., M.D.
Jesse Hafer, Jr., M.D.
*Louis A. Soloff, M.D.****
Philadelphia, Pa.

Ultrasound cardiography can record the contour of motion of the anterior leaflet of the mitral valve. In mitral stenosis and in clinically detectable mixed mitral lesions this contour is abnormal and is regarded as characteristic of and semiquantitatively related to the degree of stenosis. Similarly, in patients with pure mitral insufficiency and with congenital intracardiac defects resulting in a high flow across the mitral valve, a normal or faster than normal moving anterior leaflet has been described.[1-3] However, it would appear likely that in some patients with mitral insufficiency pathological alterations of the mitral valve structures by leaflet fibrosis, by shortening or calcification, or by chordal fusion and shortening may result in restricted motion and produce a reflected ultrasound curve mimicking or identical with that seen in mitral stenosis. It is our purpose in this report to emphasize that such indeed does occur and that even pure mitral regurgitation may be indistinguishable from mitral stenosis by ultrasound cardiography alone.

Methods

Twenty-four patients, aged 21 to 60 years, are included in this series and all were examined by one or more of the authors. Twenty-two had rheumatic heart disease, one a myocardiopathy, and one coronary artery disease. Each patient had the physical findings of pure mitral insufficiency. Phonocardiograms were recorded on each patient with a Schwarzer multichannel direct recording machine simultaneously with an electrocardiogram Lead II and indirect carotid pulse pressure curve. The phonocardiogram exhibited four frequency ranges of sound: 250 to 500, 140 to 280, 70 to 140, and 30 to 90 cycles per second. Ultrasound recordings were obtained with a Smith Kline Ekoline unit with a 2.5 megacycle crystal equipped to transmit and to receive an ultrasound signal pulsed at 200 per second. An ana-

From the Department of Medicine, Division of Cardiology, Temple University Medical Center, Philadelphia, Pa.
This work was supported in part by Grant No. HE-0663 from National Heart Institute and United States Public Health Service Postgraduate Cardiovascular Training Grant No. HE-05172.
Received for publication M[illegible] 2[illegible] [illegible].
*Associate Professor of Medicine. Present address: 6436 Fannin St., Houston, Texas 77025.
**Fellow, Division of Cardiology. Dr. Hafer performed the work during the tenure of his fellowship from the United States Public Health Service.
***Professor of Medicine; Chairman, Division of Cardiology.

logue was used to record the selected ultrasound signal directly on an Electronics for Medicine multichannel recorder simultaneously with an apexcardiogram phonocardiogram and Lead II All measurements of the diastolic descent rate of mitral valve motion were made from these tracings as previously described Ten complexes were measured from each tracing and the standard deviation for the diastolic descent rate was calculated and listed Cardiac catheterization of the right heart was performed using standard techniques. The left ventricle was entered in all patients retrogradely through the aortic valve from the right or left femoral artery Transseptal catheterization by the technique of Brockenbrough and Braunwald[14] was performed in twelve patients. Simultaneous recordings of either left atrium or pulmonary capillary pressure and left ventricle were obtained in all patients. Cine angiography employed to assess mitral valve competency was performed with a catheter passed retrogradely through the aortic valve to the left ventricular chamber from a femoral or brachial artery The degree of mitral insufficiency was estimated from the cine stud es on a zero to four plus scale. In those patients undergoing operation the surgeon s estimate of the degree of regurgitation was recorded as mild moderate or severe.

Results

Thirteen of the twenty four patients exhibited normal or faster than normal mitral valve motion by the ultrasound technique (Table I) In the remaining eleven a slower than normal rate of descent for the anterior mitral valve leaflet was demonstrated (Table II)

Of the patients in the first group (Table I) with normal mitral valve motion, mitral insufficiency was proven by cine angiography in eleven and additionally in four of these eleven at surgery In one additional patient the valvular insufficiency was confirmed by surgery alone. A typical mitral regurgitant pressure wave form was recorded in one other patient during left atrial catheterization Thus, mitral regurgitation was documented by cineangiography surgery or catheterization in all thirteen of these patients. There was no evidence from catheterization data of mitral stenosis

In addition the amplitude of valve excursion was found to be normal in eleven of these thirteen patients, and slightly diminished in two patients. In two of the thirteen patients mitral valve calcification was seen one at surgery and the other under image intensification at the time of the cine studies. In neither of these was the amplitude of excursion affected by the presence of calcification. In the six patients undergoing operation the valve leaflets were pliable, flabby and often with associated rupture of a part or all of the chordal apparatus. The phonocardiograms recorded an apical pansystolic murmur in all sixteen patients, frequently an S_3 and S_4, and an occasional middiastolic apical murmur attributed to a ventricular filling murmur which was always associated with an S_3.

Fig 1 illustrates motion of a normal anterior mitral valve leaflet. Mitral valve opening occurs 0 12 sec after S_2 and coincides with the 0 point of the apexcardiogram The diastolic downslope of the ultrasound wave, recorded during rapid ventricular filling measures and falls within the normal range (greater than 70 mm per second) Following atrial contraction, the anterior mitral leaflet floats toward and attains a nearly closed position prior to the onset of ventricular systole (upstroke of apexcardiogram after "A wave) In Fig 2 is illustrated similar findings in Patient R. A. with clinically pure mitral insufficiency There is no impairment of valvular mobility as demonstrated by the ultrasound recording The diastolic descent rate is within normal limits at 101 mm per second

Eleven of the twenty four patients exhibited anterior mitral leaflet motion less than normal ranging from 18 to 56 mm per second (Table II) Mitral regurgitation was estimated to be moderate to severe in eight patients by left ventricular cine angiographic studies and confirmed at surgery in six. Mitral regurgitation of moderate to severe degree was confirmed in an additional three patients at operation. Six patients exhibited mitral valve calcification either at surgery or fluoroscopy In those patients undergoing operation

Table I Pure mitral insufficiency by clinical examination

Normal or fast ultrasound slope

Patient age	Race sex	Diagnosis	LV angiogram	Surgical observation	Phonocardiogram	Ultrasound slope (mm/sec)	Amplitude (mm)
J W 47	Negro man	Coronary artery disease	2+ Mitral insufficiency	—	—	127 ± 14	25
R L 38	Caucasian woman	Rheumatic heart disease	3+ Mitral insufficiency moderate calcium mitral annulus and anterior leaflet	—	Apical pansystolic murmur mid-diastolic filling murmur ? O S, 0 10 sec	101 ± 6	23
R R 50	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency	Cookie bite defect anterior leaflet no calcium	Apical pansystolic murmur S_4	101 ± 14	20
F K 5	Caucasian man	Rheumatic heart disease healed subacute bacterial endocarditis	—	—	—	159 ± 18	29
M S 41	Negro man	Rheumatic heart disease	4+ Mitral insufficiency	Mobile floppy leaflet with calcium considerable mitral insufficiency	Apical pansystolic murmur ? O S, 0 10 sec	123 ± 12	32
P K 30	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency	—	Early apical systolic murmur diastolic murmur of aortic insufficiency	68 ± 3	20
J C 78	Negro woman	Rheumatic heart disease	4+ Mitral insufficiency	Redundant leaflets no calcium	Apical pansystolic murmur S_3	96 ± 11	25
D S 39	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency	Floppy leaflet anterior medial defect no calcium	Apical pansystolic murmur S_3 S_4	158 ± 4	32
E L 60	Caucasian man	Myocardiopathy	3+ Mitral insufficiency	—	Apical pansystolic murmur S_4	117 ± 6	25
M O 59	Caucasian man	Rheumatic heart disease	—	Cleft anterior leaflet ruptured chordae no calcium	Apical pansystolic murmur	124 ± 9 5	30
J W 78	Negro woman	Rheumatic heart disease	4+ Mitral insufficiency	Shortened chordae minimal calcium	Apical pansystolic murmur S_3	82 ± 12	20
J S 30	Caucasian woman	Rheumatic heart disease	2+ Mitral insufficiency	—	Apical pansystolic murmur S_4	88 ± 14	30
M C 6	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency	—	Apical pansystolic murmur diastolic filling murmur S_4 ? O	80 ± 10	37

Table II. Pure mitral insufficiency by clinical examination

Slow ultrasound slope

Patient age	Race sex	Diagnosis	LV cineangiogram	Surgical observation	Phonocardiogram	Ultrasound slope (mm./sec.)	Amplitude (mm.)
L. M. 42	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency heavy calcium	Orifice 2.5 cm. fibrous-fused leaflets with calcium in chordae shortened severe mitral insufficiency	Apical pansystolic murmur S_3 diastolic filling murmur	33 ± 3	18
P. S. 21	Caucasian man	Rheumatic heart disease	4+ Mitral insufficiency	Thickened redundant leaflets no calcium	Apical pansystolic murmur S_4	36 ± 5	26
B. G. 59	Caucasian man	Rheumatic heart disease	Mitral valve calcification on fluoroscopy	Orifice 2.0 cm. moderate mitral insufficiency heavy calcium	Apical pansystolic murmur; S_3 diastolic filling murmur	16 ± 2	11
S. G. 38	Caucasian man	Rheumatic heart disease	3+ Mitral insufficiency	Ruptured chordae fibrotic leaflets calcium specks severe mitral insufficiency	Apical pansystolic murmur S ? O.S. 0.10 sec. diastolic filling murmur	36 ± 6	26
S. M. 28	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency	Ruptured chordae leathery leaflets calcium on leaflet edges severe mitral insufficiency	Apical pansystolic murmur S_4 ? O.S. 0.10 sec.	34 ± 3	18
V. H. 23	Caucasian woman	Rheumatic heart disease	2+ Mitral insufficiency	—	Apical pansystolic murmur ? O.S. 0.10 sec.	18 ± 5	—
W. B. 28	Caucasian man	Rheumatic heart disease	Mitral valve calcification on fluoroscopy	Thickened leaflets fused commissures heavy calcium mild MS Severe mitral insufficiency	—	18 ± 1	13
K. B. 56	Caucasian woman	Rheumatic heart disease	4+ Mitral insufficiency	Thickened leaflets moderate stenosis severe mitral insufficiency no calcium	Apical pansystolic murmur diastolic murmur with presystolic accent	20 ± 2	10
J. H. 56	Caucasian woman	Rheumatic heart disease	3+ Mitral insufficiency	—	Apical pansystolic murmur diastolic filling murmur ? O.S. 0.07 sec.	31 ± 8	29
M. S. 36	Caucasian man	Rheumatic heart disease	4+ Mitral insufficiency	Thickened leaflets chordae fused no calcium, severe mitral insufficiency	Apical pansystolic murmur basal systolic ejection murmur S_3; diastolic filling murmur	43 ± 3	20
M. D. 60	Caucasian woman	Rheumatic heart disease	Mitral valve calcification on fluoroscopy	Mild mitral stenosis moderate mitral insufficiency stiffened leaflets with moderate calcification	Apical pansystolic murmur S_3 ? O.S. 0.10 sec.	49 ± 5	15

who did not demonstrate valvular calcification the valve leaflets were severely fibrotic and thickened with chordal apparatus either shortened and fused or ruptured The surgeon estimate of the mitral regurgitation was moderate to severe in every case with the additional association of a mild mitral stenosis in five of these patients Two of these five patients exhibited a mitral valve gradient at catheterization of ... Hg One patient not thought to have mitral stenosis at operation had a 5 mm mitral valve gradient at catheterization One other patient not suspected had a 5 mm mitral valve gradient at catheterization Thus seven of these patients had evidence for mitral stenosis either at operation or catheterization despite the lack of ... Four patients exhibited ... mitral stenosis. This ... all eleven patients ... mitral insufficiency ... presystolic murmur ... with or without subsequent murmur interpreted as a ... murmur In two patients, a questionable presystolic murmur in the low frequency range was recorded although not audible to any of us From the phonocardiographic standpoint this finding was thought to perhaps represent the additional lesion of mitral stenosis. In four other patients a sound with the proper timing to be an opening snap was recorded 0.10 second after the second heart sound In none of the four was this sound recognized by auscultation

Fig 3 illustrates the diastolic ultrasound descent (Patient S. G) 36 mm. per second which is abnormally slow It is accompanied by a normal amplitude of excursion A loud third heart sound coinciding with a prominent rapid filling wave on the apex cardiogram is visible At surgery this valve was fibrotic with specks of calcium No evidence for mitral stenosis was found at catheterization or surgery In contrast Fig 4 illustrates a heavily calcified valve with markedly diminished slope and amplitude (Patient W B) In this instance the heavy calcification undoubtedly contributes to the markedly diminished amplitude of excursion At operation a severe mitral insufficiency was found with a mild degree of mitral stenosis. A mitral valve gradient of 7 mm Hg was found at catheterization. This thus represents a mixed lesion though clinically it represented as pure mitral insufficiency In Fig 5 there is recorded the transseptal left atrial pressure pulse of K. B with the superimposed left ventricular pressure curve. There is severe mitral insufficiency with a large left atrial V wave and no mitral gradient The ultrasound recording (not simultaneous) suggests moderate mitral stenosis. A "slight" mitral stenosis was recorded at operation.

In 5 of the 6 patients in this group with mitral valve calcification the amplitude of excursion was 18 mm or less In three additional patients without valvular calcification amplitude of excursion was normal in two others it was slightly reduced

Fig 1 Normal mitral ... motion Upward deflection on the ultrasound (US) ... represent motion toward the transducer ... MO ... opening (MO) ... with O point on apexcardiogram (ACG) and follows S2 by 0.12 sec Mitral valve closure (MC) ... the major deflection of US ... Initial deflection ... of the ACG and US ... and follows the ... lead II of the electrocardiogram The diastolic descent ... of the US signal 13 mm per second and amplitude of deflection is 24 mm Time = 0.04 sec

Discussion

The previous observations of several investigators attests to the sensitivity of the reflected ultrasound technique in detecting normal and abnormal motion of the an

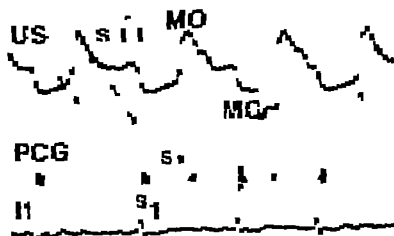


Fig 2 Patient R A T ble I M tral val lar insufficiency ith normal ltrasound (*U S*) diastolic descent rate of 101 mm. per second. The irregularities seen this slope are common in normal alves in the presence of atrial fibrillation or flutter nd presumabl result from fl ttering movements of the terior leaflet in response to flow from the trium M tral ope ing (*MO*) occurs 0 12 sec after S_2 M tral closure (*MC*) coincides with S_1 Time = 0 04 sec.

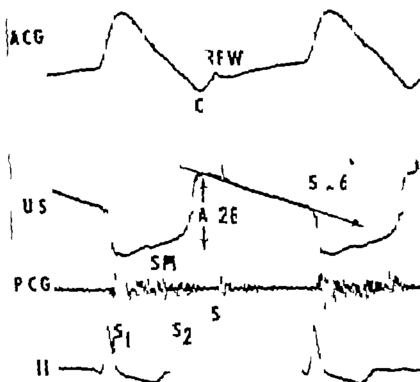


Fig 3 Patient S. G., T ble II Mitral valv lar insufficiency ith slower tha normal dia tolic de-cent rate (36 mm. per second), but th normal amplitude of excursion (26 m) Sy stolic murmur is visible in the phonocardiogram (*PCG*) and he lond S_3 coincident with the end of the pid filling (*RFW*) wave isible on the ACG Time = 0 04 sec.

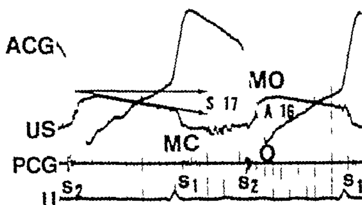


Fig. 4. P tie t W B I D, H M 1 al lar nsufficiency with very slow diastolic descent rate (17 mm per second nd de 1 pl t de of excursion (16 mm). This valve was heavily calcified and exhibited seve mit l regurg tat h m ld m t al tenosis t surgery. The rapid opening motion of the mitral valve (MO) is see t t p 1 se befor the O po t on the apexcardiogram. This is common finding in thos patient th 1 dia t l lope but never found in the presence of normal mitral valve motion. Tm 0.04 sec.

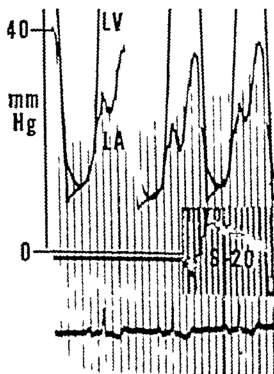


Fig. 5. Lef t al press rs LA th ec ns tructed left entric la (LV urs (nonsecutiv not multaneou). I tient h B th aortic t nosi (ES) aortic ff iene U nd mit l ficiency (A rs ms ent nth l e l m f as of sever mit l uff ienc N mit l al e g dient. Dia t lic lope f lt sound (US) 20 mm per second. Compatible th moder t ly severe m t al tenosis.

terior mitral valve leaflet.[3] In the normal the slope varies from 70 to 210 mm. per second.[3,11,4] In Fig. 1 is depicted the characteristic pattern of normal mitral valve motion. In the presence of clinically detectable mitral stenosis, alteration in valvular mobility is manifest by a slower slope during the period of rapid filling (Fig. 6). Excellent correlation has been described between the degree of stenosis as judged by calculation of valve orifice, cineangiography, and the surgical estimate when compared to the ultrasound technique.

In the presence of pure mitral insufficiency or congenital abnormalities with a high flow across the mitral valve a diastolic descent rate of normal or more rapid than normal dimensions has been reported in previous studies.[11,13] The thirteen patients in Table I of this report with pure mitral insufficiency by clinical and laboratory examination clearly demonstrate corroborative findings. In this group the diastolic descent rate of anterior mitral leaflet motion and amplitude of excursion are within or exceed the accepted limits of normal. There was no evidence for anatomic stenosis at operation in six of these patients. Nor was there evidence for stenosis by the laboratory procedures employed in the remaining seven patient

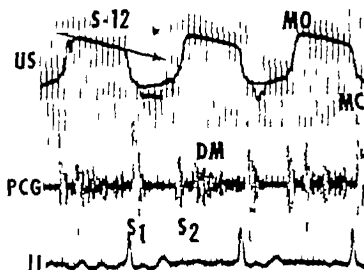


Fig. 6. Typical ultrasound (*US*) tracing in severe mitral stenosis. Diastolic descent rate (slope = 12 mm. per second) is markedly diminished and amplitude (17 mm.) moderately decreased. Loud long diastolic murmur (*DM*) visible without presystolic accentuation (atrial fibrillation). Time = 0.04 sec.

The eleven patients listed in Table II were also thought to exhibit pure mitral insufficiency by clinical criteria. In each case, however, the ultrasound study demonstrated an abnormally slow diastolic descent rate. This suggested that either a mixed lesion with some degree of anatomic stenosis but without physiologic obstruction was present, or that pathologic alteration of the valve had occurred to limit valve motion in such a manner to produce clinically pure mitral regurgitation. A mixed lesion was confirmed in seven of these patients at operation with ranges of motion from 18 to 49 mm. per second. In none of these five was the stenosis considered severe at surgery, yet the diastolic slope descent in two was in the range of severe stenosis. One of these two exhibited heavy valvular calcification, the other no valvular calcium. The other three with diastolic slopes of 33, 49, and 49 exhibited marked valvular and chordae deformity with thickening and calcification.

In an additional four patients in this group severe mitral insufficiency was the only anatomic lesion described at operation or autopsy. In each case the mitral leaflets were fibrotic, thickened, and in one case specked with calcium. Chordae were fused, fibrotic, and often occasionally ruptured.

The recording of an abnormally slow diastolic descent rate of mitral valve motion by ultrasound cardiography in apparently pure mitral regurgitation provides an additional means for the detection of mixed stenosis and regurgitation. However, it appears that pathologic distortion of the valve and chordal apparatus resulting in severe regurgitation also may be accompanied by an abnormal diastolic leaflet motion in the absence of stenosis. Thus, a slow diastolic descent rate may be due to mitral stenosis, high grade mitral regurgitation with anatomic stenosis but no physiologic obstruction, or to pure mitral regurgitation. The significance of the curves, therefore, must be interpreted in the light of other diagnostic and clinical findings. This would seem a logical finding since the extent of chronic valvulitis varies extensively from patient to patient, and it is entirely conceivable that a fibrotic shortened anterior leaflet with or without fusion or shortening of chordae may result in motion resembling that seen in stenosis alone. The great majority of patients with rheumatic mitral valvulitis do in fact exhibit mixed stenosis and regurgitation pathologically, though one or the other may dominate the picture clinically. Gustafson[11] and Edler[1] have reported that the correlation between the diastolic descent

rate and mitral valve area is not adversely affected by a certain degree of mitral insufficiency and that the technique may be useful even in the presence of mitral insufficiency in estimating orifice size. The range of diastolic descent rate of the anterior mitral valve leaflet in patients in this series with apparent pure mitral insufficiency did not permit quantitation of the degree of associated stenosis when it was present, but did permit the identification of patients with severely damaged valves from the structural standpoint.

The influence of the presence of calcification of the mitral valve apparatus on amplitude of valvular excursion and diastolic descent rate in this series is less well defined. In the thirteen patients with normal diastolic descent rates, two instances of calcification were found. The extent of calcification was slight at surgery in one and moderate at fluoroscopy in the second. Both exhibited normal amplitude and motion. Amplitude of excursion is normal in the remaining eleven.

In five of the eleven patients with abnormal diastolic descent rates, moderate to heavy calcification was found at surgery. All exhibited markedly diminished amplitude of excursion (10 to 18 mm.). Similar findings were present in one additional patient with heavy calcification on fluoroscopy. One additional patient with flecks of calcium on the mitral leaflets at surgery exhibited normal amplitude of excursion. These findings are consonant with those of Effert, Edler, and Gustafson, to the extent that the degree of calcification present may determine to a large extent the amplitude of excursion in the anterior-posterior direction of the anterior leaflet in mitral insufficiency as well as in mitral stenosis. The extent of calcification, on the other hand, reflects to some extent the degree of valvulitis present and will be found in greater extent in the more severely damaged valves. In such valves, mobility would be expected to be abnormal and reflected therefore in an abnormal diastolic descent rate as well as in decreased excursion.

It may be concluded that although the rate of movement and amplitude of excursion may be a function of the force (pressure) exerted upon the mitral valve from the atrium during diastolic filling of the ventricle, it is also dependent upon the resistance of the valve to displacement by that force. Considerable valvular distortion may take place before pressure changes occur, if they occur at all, in the atrium. Distortion of valve structures may or may not affect orifice size. It is perhaps fortuitous that correlation exists between orifice size and increased rigidity of valvular substance and structure as exhibited by ultrasound studies in patients with mitral stenosis. That this correlation is by no means perfect is demonstrated in the present study where similar reductions in rate of movement and amplitude of excursion are seen in patients with clinically apparent pure mitral insufficiency. Ultrasound studies of mitral valve motion must then be interpreted in light of clinically associated and/or physiological findings.

Summary

Mitral valve motion was studied by the reflected ultrasound technique in twenty-four patients with clinically pure mitral regurgitation. In thirteen patients mitral valve diastolic descent rate was normal or faster than normal (82 ± 12 to 200 ± 22 mm. per second) with normal amplitude of excursion (20 to 37 mm.).

Eleven patients exhibited slower than normal diastolic descent rates (18 to 56 mm. per second). Six of seven patients with extensive valvular calcification exhibited amplitudes of excursion less than 18 mm. Seven of the eleven patients were found to have minimal to mild mitral stenosis at surgery or catheterization with ultrasound slopes of 18 to 49 mm. per second, and four had no evidence of mitral stenosis.

These findings indicate that an abnormally slow ultrasound diastolic slope may be due not only to mitral stenosis but also to structural alteration of the mitral valve apparatus which produce pure mitral regurgitation or high grade mitral regurgitation with minimal or mild mitral stenosis. Diminished amplitude of excursion is related to increasing calcification regardless of whether the lesion is regurgitation or stenosis. It would, therefore, appear that correct interpretation of an abnormally low ultrasound

diastolic slope will depend upon a correla tion with other clinical and technical findings.

REFERENCES

1 Edler I and Hertz, C. H The use of ultrasonic reflectoscope for the continuous recording of movements of heart valves, Fungl. Fysiogr Sallsk. Lund Forhandl. 24:5 1954.
2 Edler L, and Gustafson, A. Ultrasonic cardiogram in mitral stenosis, Acta med. scandinav 159:85 1957
3. Effert, S Erbsen, H and Grosse-Brockhoff F The ultrasonic echo method in cardiological diagnosis, German M Month. 2:325 1957
4 Effert, S Bleifeld, W Deupmann, F J and Karitsiotis, J Diagnostic value of ultrasonic cardiography Brit J Radiol. 37:920 1964
5. Gessler R., and Samlert, H Zur Beurteilung des Ultraschallkardiogramms bei Mitral-Stenosen, Ed. 2, Kreislaufforsch 47:291 1958
6. Schmitt, W and Braun, H Mitteil ng der Mittels Ultraschallkardiographie gewonnenen Ergebnisse bei Mitral-Vitien und Herzgesunden Klin. Kreislaufforsch 49:214, 1960
7 Joyner C R Reid, J M and Bond, J P Reflected ultrasound in the assessment of mitral valve disease, Circulation 27:503 1963
8 Segal, B. L. Likoff W and Kingsley B Echocardiogr phy Clinical application in mi tral stenosis, J A M A 195 161 1966.
9 Winters, W L J Riccetto, A Gimenez, J M Donough, M nd Soulen, R. Assessment of reflected ultrasound as a diagnostic instrument in the study of mitral valve disease, Brit. Heart J 29 788, 1967
10. Grossman, C. C., Holmes, J H Joyner C., and Purnell, E. W Diagnostic ultrasound. Proceedings of the First International Confer ence New York, 1966, U iv of Pittsburgh Plenum Press.
11 Gustafson A. Ultrasound cardiography in mitral stenosis, Acta med. scandinav Suppl. 461 1966.
12. Segal, B L Likoff W and Kingsley B. Echocardiography Clinical application in mitral regurgitation, Am. J Cardiol. 19:50, 1967
13 Ultan L B Segal, B L and Likoff W Echocardiography in congenital heart disease Preliminary observations, Am. J Cardiol. 19 74 1967
14 Edler I. Mitral valve function tudied by the ultrasound ech method, Grossman, C C. Holmes J H Joyner C and Purnell, E. W editor Diagnostic ultrasound. New York, 1966, Plenum Press, pp 198-228.
15 Brockenbrough E. C and Braunwald, E. A new technic for left ventricular angiocardiog raphy and transseptal left heart catheteriza tion, Am. J Cardiol. 6 1062, 1960.
16. Effert, S Pre and postoperative evaluation of mitral stenosis by ultrasound, Am. J Car diol. 19:59 1967
17 Effert, S Der derzeitige Stand der Ultra schallkardiographie, Arch. Kreislaufforsch. 30 214, 1959
18 Edler I Ultrasound cardiography in mitral valve stenosis, Am J Cardiol. 19 18, 1967
19 Gustafson, A Correlation between ultrasound cardiography hemodynamics and surgical findings in mitral stenosis, Am. J Cardiol 19:32, 1967

Experimental and laboratory reports

Comparison of right atrial and right ventricular single and paired pacing in the canine heart

*David Thomas Kelly M B Ch B M R A C.P.**
Cape Town South Africa

Right ventricular (RV) pacing either from an endocardial catheter[1] or epicardial electrodes are the usual methods of sustained electrostimulation of the heart When this is used asynchrony of contraction occurs between atrium and ventricle and normal atrial transport function is lost. Because of this atrial triggered pacemakers have been designed and used[3] The atrial contribution to ventricular output has been shown to be important in the isolated preparation during fast and slow rates experimentally[4] and in patients with myocardial decompensation When no disease is present and the cardiovascular system intact, the transport function of the atrium is thought to be unimportant but most physiological experiments[7,8] suggest that asynchronous pacing lowers stroke volume and external stroke work.

Paired pacing is where the heart is repetitively excited by 2 selectively spaced electrical stimuli. The first will cause depolarization and mechanical contraction and the second occurring after the absolute refractory period results in a second depolarization but is mechanically ineffective. This is known as postextrasystolic potentiation (PESP) and is a powerful inotropic stimulus. This phenomenon has been observed in mammalian heart muscle for many years. The history and development has been reviewed by Cranefield[9,10]

PESP can only be satisfactorily elicited from the ventricles[1] as when the 2 stimuli are applied to the atrium the second may be delayed in the A V node and fail to depolarize the ventricle. Paired pacing does not increase the output and external work of the normal heart, but strikingly improves the hemodynamic parameters in the failing heart[11] Little data, however is available on the effect of paired pacing in the normal heart when it is suddenly exposed to a stress which is insufficient to cause decompensation.

The purpose of this report is to compare the effects of right atrial (RA) pacing with single and paired RV pacing and to see if any further hemodynamic differences could be detected during increased afterload

Method

Sixteen mongrel dogs weighing between 15 and 24 kilograms were studied. Each dog underwent right thoracotomy under

From the Cardiac Clinic, Department of Medicine Groote Schuur Hospital and the University of Cape Town, and the Cardiovascular Pulmonary Research Group supported in the Department of Medicine by the Council for Scientific and Industrial Research.

Supported by grant from the Cardiovascular Pulmonary Research Group Council for Scientific and Industrial Research.

Received for publication Jan 26 1968

*Research Fellow Cardiovascular Pulmonary Research Group.

thiopentone anesthesia. The pericardium was opened and alcohol injected into the region of the sinus node which was later crushed and sutured to achieve sinus arrest. Pacemakers were sewn to the superior right atrium and the anterior surface of the right ventricle. The dogs were allowed to recover and between 24 and 48 hours later were anesthetized with 15 mg. per kilogram of pentobarbitone initially and maintained on a constant infusion of approximately 0.05 mg. per kilogram per minute throughout the experiment. All the dogs were intubated and breathed O_2 spontaneously through a Manley respirator. Catheters were placed in left ventricle and thoracic aorta for recording pressures via a Statham P23D strain gauge with zero point 8 cm. above the table top; the first derivative of the left ventricular pressure was recorded via the catheter on a R.C. differentiating circuit. The percentage change of the peak level with different pacing was calculated. These plus the electrocardiograms were recorded photographically on a N.E.I. Honeywell recorder. Cardiac output was measured after an injection of 1.25 mg. of cardiogreen into the right atrium via a catheter and a constant volume syringe (Clay Adams Aupette) and sampling via a femoral artery using a Waters densitometer X302 with a Sanborn computer and constant withdrawal (38.9 c.c. per minute) Harvard pump. All blood was reinfused. The densitometer and computer were previously calibrated using the dog's blood and a preselected dye concentration. At the end of the experiment, a further calibration with the dog's blood was done to assess if the effect of background dye was important. The heart was paced at 3 milliamperes using a transistorized battery driven pulse generator capable of delivering single or paired stimuli (Medtronics Inc. Model 583A). Throughout each experiment the rate was constant.

In 8 dogs, after 4 minutes of right atrial single pacing (RAsp) dual outputs, left ventricular pressure and its first derivative dp/dt, the left ventricular end-diastolic pressure and aortic pressure were recorded. Single pacing was then commenced from the RV electrode (RVsp) and after 4 minutes the same records were taken. Following this, RAsp was restarted and observations made to ensure that a steady state persisted. The sequence was repeated except that right ventricular paired pacing (RVpp) replaced RVsp.

When the 3 types of pacing had been measured in the control state angiotensin was infused to increase the afterload and after 8 minutes, when the pressure had increased significantly and was stable, all measurements were again recorded during the types of pacing. In order to ensure that changes in the types of pacing did not alter the circulatory state of the dogs 8 further animals were similarly studied except that only 2 types of pacing were compared in the same manner (i.e., 4 RAsp to RVsp and 4 RAsp to RVpp before and during angiotensin).

In all dogs, single RV pacing was possible without atrial interference and paired pacing was accomplished with a stimulus interval between 160 and 210 msec. at 5 volts which was usually twice the diastolic threshold. After cessation of paired pacing

Table I. RA and RV single pacing (mean value in 12 dogs)

Type of pacing	Aortic pressure	LVED pr.	Stroke vol.	Stroke work
RA	100	1.7	24	32
RVsp	92	2.1	21	25
Angiotensin				
RA	144	3.5	24	46
RVsp	135	3.5	21	38
P values	<0.001	<0.001	<0.001	<0.001

Table II. RA single and RV paired pacing (mean values in 12 dogs)

Type of pacing	Aortic pressure	LVED	Stroke vol.	Stroke work
RA	94	1.9	23	27
RVpp	93	1.1	23	27
Angiotensin				
RA	139	2.6	23	43
RVpp	140	1.6	24	44
P value	>0.05	<0.001	>0.05	>0.05

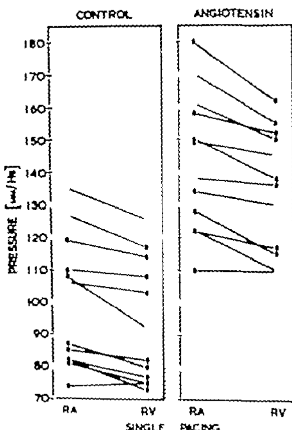


Fig. 1A. The difference in pressure between RA and RV single pacing during control and angiotensin (afterload).

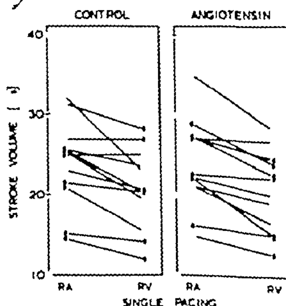


Fig. 1B. The difference in stroke volume between RA and RV single pacing during control and angiotensin (afterload).

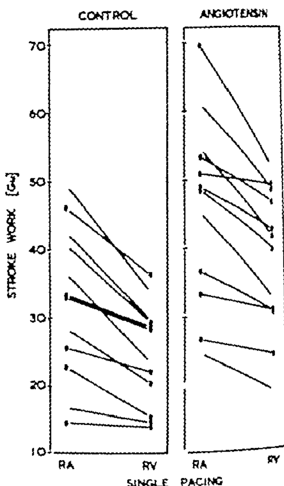


Fig. 1C. The difference in stroke work between RA and RV single pacing during control and angiotensin (afterload).

when RAsp was substituted the blood pressure dropped and the end-diastolic pressure rose transiently but returned to normal within 2 minutes. As no difference was noted between dogs who had 3 types of pacing and dogs who had only 2 result were pooled giving 12 in each category. From the figures for cardiac output systemic mean pressure left ventricular end diastolic pressure and rate stroke volume and stroke work were calculated from the following formula

$$\text{Stroke work (Gm/M)} = \frac{\text{SV (MAP} - \text{LVEDP)} \times 1.36}{100}$$

where SV stroke volume c.c., MAP mean aortic pressure mm Hg and LVEDP left ventric[illegible] astolic pressure mm Hg [illegible] puration

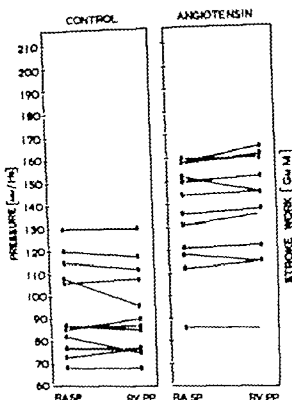


Fig 2A The difference in pressure bet een RAsp and RVpp during control and angiotensin infusion.

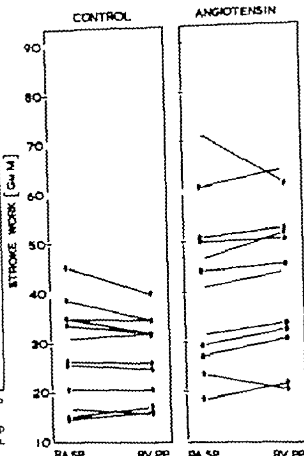


Fig 2B The difference in stroke olume bet een RAsp and RVpp during control and ngiotensin infusion.

The mean aortic pressure was measured by electrical integration

Results

Results for RA to RV single pacing are shown in Table I and for RA to RV pa red pacing in Table II

In Fig 1*A* where RA pacing is compared to single RV pacing in 12 dogs, the blood pressure decreases slightly with a mean drop of 7 2 mm Hg (1 to 16 mm Hg range) and after angiotensin 8.7 mm Hg (0 to 18 mm. Hg range)

Stroke volume (Fig 1*B*) is similarly compared and the average decrease is 14 per cent. This is unchanged by angiotensin. Stroke work (Fig 1*C*) shows a further decrease of 35 per cent control and 37 per cent angiotensin The average rise in LVED pressure with RV single pacing is 0.46 and 0 44 mg with increased afterload and the percentage decl ne of dp/dt was 14 and 16 per cent, respectively Thus in all measured parameters, the RA pacing was superior to RVsp and n terms

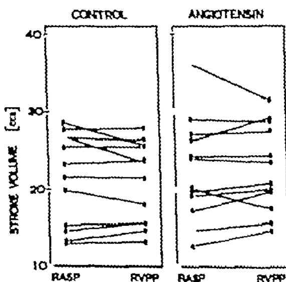


Fig. 2C. The difference in stroke work bet een RAsp and RVpp during control nd angiotensin infusion

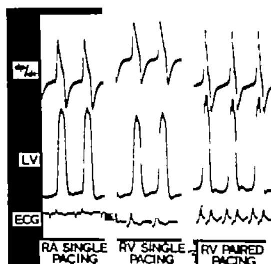


Fig 3 Left ventricular pressure pulses and dp/dt during the types of pacing RV single pacing shows a slight decline in peak pressure and dp/dt. RV paired pacing shows enhancement as compared to RA and a small second mechanical event is seen on the LV pulse

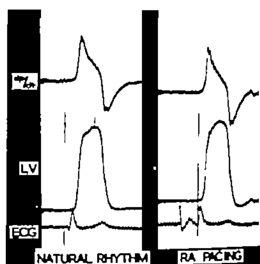


Fig 4 Showing natural rhythm when no electrical event to cause the normal P wave in the atrium is seen and after atrial pacing when it reappears.

of stroke work this is statistically significant

When RA pacing is compared to RVpp before and after angiotensin no striking differences are seen Average systemic pressure (Fig 2A) dropped by 1 3 and 0 5 mm. Hg when afterload was applied. Stroke volume (Fig 2B) increased by 3 and 6 per cent and stroke work (Fig 2C) by 5 5 and 8 per cent. All this variation is within the limits of experimental error and is not statistically significant.

The first differential of the left ventricular pressure however showed a 20 per cent increase with paired pacing and increased to 30 per cent when afterload was present.

The end-diastolic pressure declined 1 1 and 1 5 mm. Hg during increased afterload

The types of pacing are illustrated in Fig 3

Discussion

The cardiac output may fluctuate widely in anesthetized dogs.[13,14] Pentobarbitone was used as the anesthetic and while this had an anticholinergic action it does not interfere greatly with the sympathetic system [13,14]

The dog was lightly anesthetized to avoid significant myocardial depression and a slow continuous infusion was used to achieve a steady state About 1 hour after induction of anesthesia, the output was stable and thus measurements could be commenced The dogs were allowed time to recover from the operation to prevent further variations in output due to recent thoracotomy The sinus node was obliterated so that paired and single pacing could be established at the same slower rate also without electrical stimulation no significant atrial contraction was seen (Fig 4) Thus, the atrial pacemaker when used could control the rate and cause synchronous atrial mechanical contraction but when RV pacing was instituted no significant variation in the left ventricular pressure pulse usually seen in asynchronous pacing could be found

When external stroke work is used as a parameter of myocardial function, the rate must be constant otherwise, the spontaneous fluctuation in rate found in the anesthetized dog plus bradycardia caused by increased afterload will cause a very significant change in stroke volume due to rate alone and invalidate comparisons which should depend on output changes. Accordingly the rate was constant throughout the experiment.

Angiotensin was used to increase the

afterload and provide significant ventricular stress. While this drug has some inotropic action in the papillary muscle preparation[7] when the cardiovascular system is intact, there is no significant myocardial or venous action.[8] The drug is short-acting and has no significant tachyphylaxis during an acute experiment.

The amount of drug infused varied between 4 to 14 μg per minute depending on the weight and individual response of the dog. The blood pressure was elevated to a single constant level in each experiment between 25 and 70 mm. Hg above control levels.

When a normal ventricle is subjected to an increased afterload the rate slows and output falls, the heart dilates and the end-diastolic pressure rises. If the load is within the range of physiological compensation all these tend to return to normal.[19] This decline in LVED pressure with increment of aortic pressure is thought to reflect decreased ventricular size and increased contractility.[21] Recent work suggests, however, that part of this decline may be due to stress relaxation of series viscous components of the ventricle consequent on increased afterload.[22] From serial observations, it was found that in 8 minutes a steady state was reached and measurements were taken after this.

When RVsp was used blood pressure and stroke volume declined. As the numerical value of LVED pressure is small in comparison with systemic mean pressure stroke work reflects mainly these 2 parameters. In this preparation during an acute experiment, therefore, stroke work is less and thus the loss of atrial contraction is a significant factor. Pacemakers applied to different anatomical sites in the ventricle may cause variation in hemodynamic findings.[23] The abnormal depolarization of the right ventricle from an epicardial electrode on the anterior surface may be responsible for a less efficient contraction than that initiated through the normal conducting pathway. This may cause some asynergy of contraction of the left ventricle and may contribute to the lower hemodynamic findings. Using the present experimental technique, however, the contribution of this factor cannot be assessed.

In both control and afterload heart, the difference was of the same order showing that stress within the range of physiological compensation did not further aggravate the differences caused by loss of atrial contraction. When RA pacing is compared to RVpp no significant difference is seen. From Fig. 2C it would appear that paired pacing confers slight benefit during afterload but this is not statistically significant. Other experiments, where afterload is increased sufficiently to cause decompensation show that paired pacing results in a marked improvement. When a comparison is made between RV paired and single pacing because the stroke work is the same as RA pacing paired pacing is hemodynamically better than single pacing. In both types of RV pacing atrial contraction is not a contributory factor. The dp/dt is increased and the LVED pressure decreased with paired pacing suggesting that the velocity of contraction plus diastolic compliance or end-diastolic volume has altered. This is a known result of paired pacing. The decline in dp/dt seen with RVsp is due to multiple factors, among them a lower systemic pressure, an abnormal ventricular depolarization plus the loss of atrial transport function.

The inotropic stimulus of PESP will only compensate for the loss of atrial contraction in the normal heart and will not elevate output or pressure above this. Because PESP causes moderate increase in oxygen consumption[23] which in turn reflects enhanced velocity of contraction[24] and as external work is not increased, normal rhythm with synchronous atrial contraction will be more efficient even when the sinus node is not destroyed as in this preparation because repetitive ventricular stimuli will be conducted retrograde to depolarize the sinus node and interfere with atrial contraction.[17] Paired pacing while altering the force-velocity characteristics of muscle contraction,[24] produces no improvement of the heart, as judged by its external work as a pump, when the myocardium is normal or when significant physiological stress which can normally be compensated for is present, thus this powerful inotropic stimulus serves no useful purpose.

This is also found with the digitalis

glycosides which apart from the rise in oxygen consumption found with paired pacing tend to produce similar effects when given in therapeutic dosage

Measurable improvements found in the failing heart with powerful inotropic stimuli cannot be demonstrated in the normal situation The intricate regulatory systems which maintain pressures and flows at optimal levels in spite of stress such as change in afterload is a homeostatic mechanism[1] which nullifies the effect of PESI which would otherwise upset the normal hemodynamic balance

Summary

Sixteen mongrel dogs were previously prepared by destruction of the sinus node at right thoracotomy to obliterate significant atrial contraction and pacemakers were implanted in the right atrium and right ventricle

After surgical recovery the dogs were anesthetized with pentobarbitone Aortic pressure left ventricular pressure plus its first derivative were measured Cardiac output was sequentially determined using a Waters densitometer and Sanborn computer via a femoral artery sampling of indocyanine green injected into the right atrium

Stroke volume and work were calculated during single pacing of the right atrium and right ventricle and during paired pacing of the right ventricle all at constant rates. The 3 types of pacing were measured at rest and during infusion of angiotensin to increase the afterload

Results show that single RA pacing is hemodynamically superior to single RV pacing in all instances as greater stroke volume and work is achieved and the difference is due to loss of atrial contraction During increased afterload within the limit of physiologic compensation no further difference was found

Paired pacing of the right ventricle lowers the LVED pressure and increases dp/dt of the left ventricular pulse but stroke work is the same as seen with RA pacing

The inotropic stimulus of paired pacing compensates for the acute loss of atrial contraction as seen with RV pacing but even with increased afterload no further improvement is detected in the normal myocardium

I wish to thank Professor V Schrire and Professor C. N Barnard for their help and encouragement and Miss E. E. Firth for her technical assistance

I am most grateful for the financial support received from the Council for Scientific and Industrial Research. This work was done during the tenureship of a C.S.I.R Senior Research Officer post in the Cardiovascular Pulmonary Research Group

REFERENCES

1 Harris, A Bluestone R., Busby E., Davies G Leatham A. Siddons, H., and Sowton E. The management of heart block, Brit. Heart J 27:469 1965.
2. Chardack, W M Gage A. A., and Greatbatch W Correction of complete heart block, J Thoracic & Cardiovas. Surg 48:814 1964.
3 Nathan, D A. Center S. Samet P and Wu C Y The application of an implantable synchronous pacer for the correction of Stokes-Adams attacks, Ann. New York Acad Sc 111 1093 1964.
4 Gilmore J P Sarnoff S. J Mitchell, J H and Linden, R J Synchronicity of ventricular contraction Observations comparing haemodynamic effect of atrial and ventricular pacing Brit Heart J 25:299 1965.
5 Nakano, J Effects of atrial and ventricular tachycardia on the cardiovascular dynamics Am J Physiol. 206:547 1964
6 Bechimol, A Ellis, J G and Grey Dimond, E. Haemodynamic consequences of atrial and ventricular pacing in patients with normal and abnormal hearts, Am. J Med. 39:911 1965.
7 Snyder J and Wood, F H.: The effects of heart rate on atrial contribution to cardiac output in dogs with complete heart block, Fed Proc 1 137 1962.
8 Martin, R H Cobb, A Lau, S. H., and Swanson, W E. Reduction of cardiac output caused by asynchronous ventricular pacing in ... Circulation 30 122 1964
9 Cranefield, P F The force of contraction of extrasystoles and the potentiation of force of the postextrasystolic contractions a historical review B ll. New York Acad. Med. 41:419 196.
10. Cranefield, P F Paired pulse stimulation and postextrasystolic potentiation Prog Cardiovas Dis. 8:446, 1966.
11 Katz, L N Effect of artificially induced paired and coupled beats, Bull. New York Acad Med 41 428 1965
12. Goetz, R H Jallah, E. M and Goetz, V M Circulatory dynamics of paired pacing in hypotensive and cardiogenic shock, Am. Heart J 3:506 1967
13 Howell C D and Horvath, S. M The reproducibility of cardiac output measurements in the dog J Appl. Ph iol. 14 421 1959
14 Vogt D C Honusek C Schleve J F H... H B and Sapperstein, L. A. Simultaneous ...

ability of cardiac output in the dog, Am. J Physiol. 181:337 1955

15. Nash C. B Davis, F and Woodbury R. A. Cardiovascular effects of anaesthetic doses of Pentobarbital sodium, Am J Physiol. 185 107 1956.
16. Shabetai, R., Fowler N O and Hurlburt, O Hemodynamic studies of dogs under pentobarbital and morphine chloralose anesthesia, J Surg Res. 3:263, 1963
17. Koch-Weser J The nature of the inotropic action of angiotensin on the ventricular myocardium, Circulation Res. 16:230, 1966.
18. Fowler N O and Holmes, J C Coronary and myocardial actions of angiotensin, Circulation Res. 14 191 1964.
19. Olmsted, F and Page I H *Haemodynamic* aspects of prolonged infusion and angiotensin into unanaesthetized dogs, Circulation Res 16:140, 1965.
20. Goodyear A. V N Goodkind, J and Landry A. B. Ventricular response to pressure load, Circulation Res. 10:885 1962.
21. Sarnoff S. J Mitchell, J H Gilmore, J P and Remensnyder J P Homeometric autoregulation in the heart, Circulation Res 8 1077 1960.
22. Sonnenblick, E H Ross J Covell J W and Braunwald, E Alterations in resting length tension relations of cardiac muscle induced by changes in contractile force, Circulation Res. 19:980, 1966.
23. Lister J W Klotz, D H., Jomain S. L., Stuckey J H and Hoffman, B. F Effect of pacemaker site on cardiac output and ventricular activation in dogs with complete heart block, Am J Cardiol 14:494, 1964
24. Bartelstone, H J Scherlag, B. J Hoffman, B F and Cranefield, P F Demonstration of variable diastolic compliance associated with paired stimulation of the dog heart, Bull New York Acad. Med 41:616, 1965
25. Ross, J J Sonnenblick, E. H Kaiser G. A Frommer P L and Braunwald, E. Electroaugmentation of ventricular performance and oxygen consumption by repetitive application of paired electrical stimuli, Circulation Res. 16:332, 1965
26. Sonnenblick, E H Ross, J Covell, J W Kaiser G A and Braunwald, E. Velocity of contraction as a determinant of myocardial oxygen consumption, Am J Physiol 209:919 1965.
27. Sarnoff S J Gilmore J P Daggett, W M Mansfield P B McDonald, R H. J and Weisfeldt, N L Net potassium loss and changes in oxygen and ventricular performance during paired stimulation of the heart, Bull New York Acad. Med 41:602, 1965

The effects of meperidine, promethazine, and chlorpromazine on pulmonary and systemic circulation

Stanley J. Goldberg, M.D.
Leonard M. Linde, M.D.
Robert R. Wolfe, M.D.
William Griswold, M.D.
Kazuo Momma, M.D.
Los Angeles, Calif.

Since the introduction of the combination of meperidine promethazine and chlorpromazine (MPC) (Demerol Phenergan and Thorazine) the need for general anesthesia during cardiac catheterization has become infrequent.[1] Inherent in the adoption of this drug combination is the assumption that it exerts little influence on cardiopulmonary hemodynamics. This basic assumption has received little critical investigation. The individual agents are known to produce changes in systemic hemodynamics.[2-4] We have noted that meperidine alone produces significant changes in pulmonary circulatory dynamics.

The purpose of this study was to determine the effects of MPC in animals under controlled conditions in the hope that the information might help in the prediction of changes in human beings during cardiac catheterization.

Methods

A total of 21 mongrel dogs weighing between 15 to 20 kilograms were prepared as follows. Under sterile conditions, a thoracotomy was performed and polyvinyl catheters were sewn into the left atrium, pulmonary artery, and a systemic artery. An electromagnetic flow probe was placed around the ascending aorta to measure aortic blood flow (assumed to be equal to pulmonary blood flow without correction for coronary circulation). Catheters and flow probe wires were tunnelled to exit from the posterior neck. After the operation, catheters were filled with heparin to prevent clotting and the animals were permitted to recover for 1 to 2 weeks until blood pressures and cardiac output stabilized. Dogs were trained to lie prone for extended periods of time. Only a single drug or MPC was tested in any animal during any 24-hour period. Agents were infused into the main pulmonary artery over a 60- to 90-second interval. Pulmonary artery, left atrial and systemic pressures, and stroke velocity were recorded during a control period and following administration of one of the following drug combinations: (1) 1 or 2 mg. per kilogram of promethazine (2) 1 or 2 mg. per kilogram of chlorpromazine (3) 2 mg. per kilogram of meperidine and (4) a combination consisting of 2 mg.

From the Division of Cardiology, Department of Pediatrics, UCLA School of Medicine, Los Angeles, Calif. 90024
Supported by funds from the United States Public Health Service.
Received for publication Feb. 7, 1968.

per kilogram of meperidine 1 mg per kilogram of promethazine and 1 mg per kilogram of chlorpromazine. Pulmonary artery and left atrial pressures were measured with P23BB transducers and systemic pressure was measured with a P23DE transducer. In all animals, measurements of arterial pO_2, pCO_2, and pH were obtained prior to drug administration and intermittently following infusion of the test agent. Stroke velocity was measured with a gated square wave flowmeter and cardiac output was obtained by electrical integration of stroke velocity. Accuracy of flow measurement was confirmed by indicator dilution techniques. Zero flow was obtained electrically by a circuit which determined the pre-ejection flow velocity in the aorta and established that level as zero flow. Experiments were analyzed only if the flow signal had a stable base line. Transducer and flowmeter outputs were monitored on a photographic oscillograph. Peak stroke velocity was measured. Pulmonary vascular pressure gradient was computed by subtracting left atrial from pulmonary artery pressure. Pulmonary vascular resistance was computed by dividing pulmonary vascular pressure gradient by cardiac output. Total systemic vascular resistance was computed by division of systemic pressure by cardiac output.

The individual experiment control value for each parameter was computed by sampling each parameter at 1-minute intervals during a stable 10-minute control period. The individual experiment control value for each parameter was established by computing the mean and standard deviation of the 10 control determinations. After injection of the test agent, the value of each parameter was compared to its own control every minute during the 60-minute experiment, and the percentage difference between the experimental and control value was computed for each minute. The statistical significance of change in each parameter for each minute was determined by combining all experiments for each minute for each drug and dosage level and considering all controls to be 0 per cent change. The mean percentage change for each minute was then analyzed to determine if the change was statistically significant ($p < 0.05$). The group mean control value for each parameter was determined by computing the mean of the individual experiment control values.

*Mederpotenum.

Results

Sleep was never produced by the individual agents or the combination. However, the animals remained mildly sedated for 40 to 60 minutes following the infusion.

Mean changes in pH, pCO_2, and pO_2 following drug infusion were minimal and not statistically significant.

Sham infusion. No statistically significant change in any parameter occurred during the hour following infusion of 0.9 per cent of saline into the pulmonary artery.

Meperidine, 2 mg. per kilogram, was infused in 10 experiments in 5 dogs. Meperidine produced an immediate and sustained decrease in cardiac output (30 per cent) secondary to a decrease in both stroke volume and heart rate. Calculated pulmonary vascular resistance and systemic vascular resistance were significantly increased (Fig. 1).

Promethazine, 1 mg. per kilogram, was tested in 14 experiments in 8 dogs (Fig. 2). There was a significant increase in calculated pulmonary vascular resistance despite a marked rise in cardiac output. Heart rate increased significantly and remained elevated 20 per cent throughout the period of observation. Since heart rate increased proportionately more than cardiac output, stroke volume decreased significantly during the first 10 minutes but then returned to approximately control levels after 30 minutes. Systemic arterial pressure remained relatively unchanged during the first five minutes but then was significantly elevated between the fifth and tenth minute postinjection.

Promethazine, 2 mg. per kilogram, was evaluated in 12 experiments in 7 dogs (Fig. 2). Infusion of a higher dose of Phenergan produced a marked increase in pulmonary artery pressure with a 90 per cent increase at the end of the first minute. Calculated pulmonary vascular resistance was significantly increased throughout the experiment. Cardiac output increased immediately but not significantly and remained

elevated throughout the remainder of the experiment. Systemic arterial pressure was highly significantly elevated (approximately 30 per cent) and remained elevated throughout the experiment. Systemic vascular resistance was also elevated. Heart rate was considerably elevated and the mean change was approximately 40 per cent. Since cardiac output increased less than heart rate, stroke volume fell significantly and remained *below control level.* Peak stroke velocity and stroke accelera-

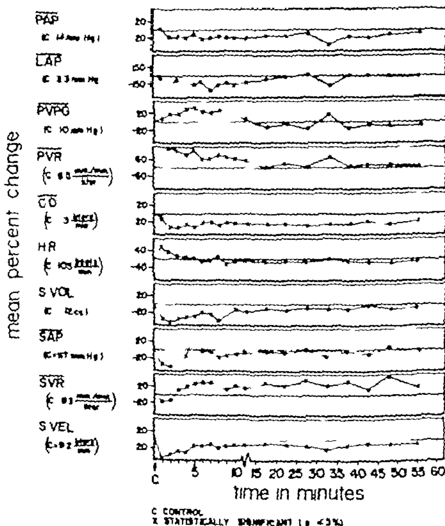


Fig. 1. Mean percentage changes from control following infusion of meperidine 2 mg. per kilogram (vertical axis) are plotted against elapsed time since infusion (horizontal axis). The control value (*C*) is indicated as 0 per cent change on the individual graphs. The mean control value was established for individual experiments by determining the mean value of each *parameter for each of the 10 minutes preceding drug infusion.* Percentage deviations following injection were determined by comparing each experimental minute value to its mean control. The mean percentage change each minute was tested statistically to determine the significance of change from control. "X" for a minute or group of minutes indicates that the mean value was significantly different from control ($p < 0.05$). The numerical control value under the parameter name is the mean of the individual experimental control means (From Goldberg, Linde, Gaal and Sack: The pulmonary and systemic hemodynamic effects produced by meperidine and its derivatives. J. Pharmacol. & Exper. Therap. 306 157, 1968.)

$\overline{PAP}$, Mean pulmonary artery pressure; $\overline{LAP}$, mean left atrial pressure; $\overline{PVPG} = \overline{PAP} - \overline{LAP}$; $\overline{CO}$ ... stroke velocity = cardiac output; PVR, $\overline{PVPG}/\overline{CO}$ = pulmonary vascular resistance; HR, heart rate; S.V., $\overline{CO}$/HR = stroke volume; $\overline{SAP}$, mean systemic arterial pressure; SVR, $\overline{SAP}/\overline{CO}$ = systemic vascular resistance; S. Vel., stroke velocity; S. Acc., stroke acceleration = dS Vel./dt.

tion were both significantly decreased throughout the entire experiment.

Chlorpromazine 1 mg per kilogram was evaluated in 10 experiments in 6 dogs (Fig 3) One mg per kilogram of Thorazine produced a striking increase in cardiac output and a secondary calculated decrease in pulmonary vascular resistance. Systemic pressure fell significantly (approximately 15 per cent) throughout the entire experiment and cardiac output was increased by approximately 20 per cent Systemic vascular resistance was, therefore decreased by approximately 30 per cent throughout most of the experiment. Heart rate changed only slightly and therefore, stroke volume increased as the result of an increase in cardiac output. Peak stroke velocity remained diminished during the entire experiment but stroke acceleration remained near control

Chlorpromazine 2 mg per kilogram was evaluated in 9 experiments in 5 dogs. Pulmonary artery pressure was diminished throughout the experiment but in the presence of a markedly increased cardiac out

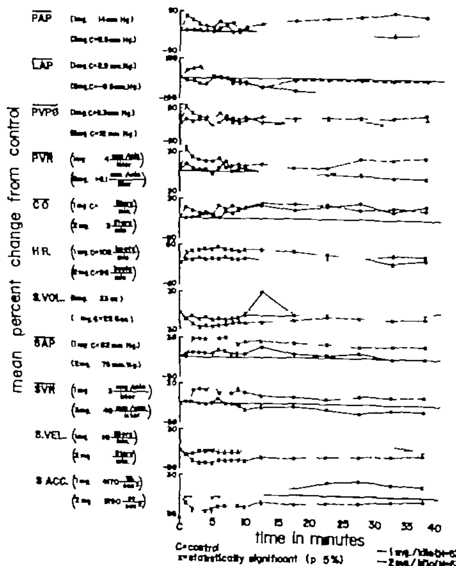


Fig 2 Mean percentage changes from control following infusion of promethazine 1 and 2 mg per kilogram (See Fig 1 for legend.)

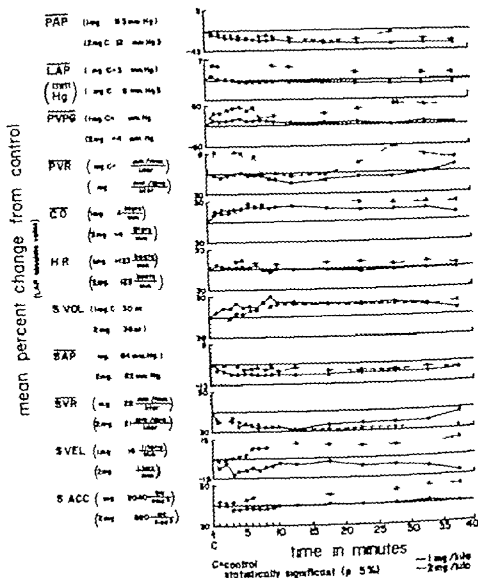


Fig. 3. Mean percentage changes from control following infusion of chlorpromazine 1 and 2 mg. per kilogram. (See Fig. 1 for legend.)

put calculated pulmonary vascular resistance was increased throughout the experiment.

Meperidine 2 mg per kilogram promethazine, 1 mg per kilogram and chlorpromazine 1 mg per kilogram was evaluated in 15 experiments in 8 dogs. Calculated pulmonary vascular resistance increased up to 60 per cent and systemic resistance fell approximately 70 per cent with cardiac output near control levels during the latter 30 minutes of the experiment. Tachycardia was observed and stroke volume and stroke velocity fell significantly.

Discussion

Controlled investigation of the cardiovascular effects of MPC in experimental animals or human beings has not been performed previously. Recent investigators however have demonstrated that parenterally administered MPC decreases oxygen consumption and enhances the tendency of the sick infant to develop metabolic acidosis.[3] The data presented herein was not affected by either of these factors as cardiac output was actually measured and no significant alterations in pH, pCO_2 and pO_2 occurred.

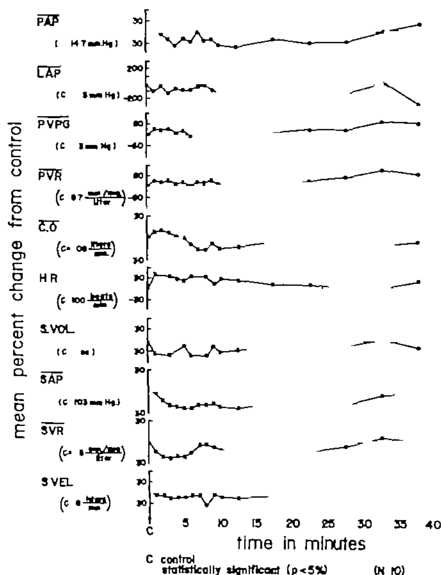


Fig. 4 Mean percentage changes from control following infusion of demerol, 2 mg. per kilogram phenergan 1 mg. per kilogram, and chlorpromazine, 1 mg. per kilogram. (See Fig. 1 for legend.)

Little is known about the cardiovascular effects of the individual agents. Meperidine has been proported to be a systemic and coronary artery dilator and a vagolytic agent. [8] Chlorpromazine produces systemic vasodilation due to central and local (-adrenergic) mediators and causes cardio-acceleration. The cardiovascular actions of promethazine have not been characterized.

MPC was studied by Shackman and associates[1] in 15 adult patients. Tachycardia and decreased systemic resistance were observed. Pulmonary circulatory parameters were not evaluated. Smith and co-workers[1] studied 670 patients and reported that MPC produced no consistent changes in systemic or pulmonary arterial pressure. Pulmonary and systemic blood flow and thus, resistance were not measured. Unsatisfactory results at catheterization because of tachycardia, hypotension, and restlessness have been described.[11]

The dosage of MPC given was 2, 1, and 1 mg per kilogram respectively which is similar to the CM mixture (2.2, 0.7 and

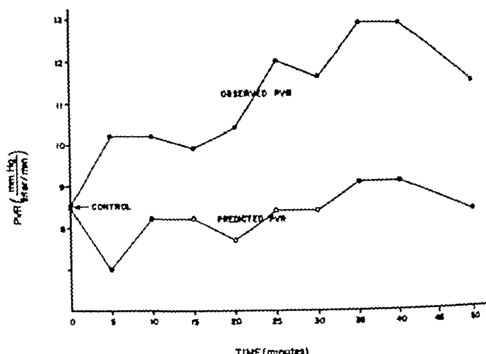


Fig 5 The ope[illegible] rcle represent predicted PVR (based on flow-resistance regression equation see text [illegible] the same flow [illegible] ompar ble po[illegible] t for observed PVR (closed circle). Difference between the 2 lines (Δ PVR) epresent act[illegible] soc nst ict on

0 7 mg per kilogram) of the Toronto group. In our preparation maximal effects on pulmonary vascular resistance were observed at 60 minutes or longer after intravenous administration It is of interest that the magnitude and direction of systemic effects in our chronic dogs were virtually identical to those in human beings studied by Shackman and associates

The potentially important implication of our study is the effect of MPC on pulmonary vascular tone As pointed out by Rudolph and Auld [11] calculated pulmonary vascular resistance assesses only resistance to flow but does not provide information regarding vascular tone For example increased pulmonary blood flow mechanically distends the pulmonary vascular bed and passively decreases calculated pulmonary vascular resistance A regression equation derived from Rudolph's data for dog lungs was used to predict pulmonary vascular resistance at various flow rates (passive effects) and observed pulmonary vascular resistance at the same observed flow rate in our preparation revealed a substantially increased pulmonary vascular resistance over predicted values. This Δ pulmonary vascular resistance must be due to active vasoconstriction of the pulmonary vascular bed (Fig 5) This analysis of the data indicates that of the individual components promethazine and chlorpromazine were responsible for the active vasoconstriction, whereas meperidine primarily caused decreased cardiac output which passively increased pulmonary vascular resistance.

It is apparent that the effects observed in dogs may not be directly transferable to humans since there may be species, dosage, and timing differences as well as a different route of administration. However previously reported systemic vasodilator effects of intramuscular MPC in humans[7] are similar to the systemic vasodilator effects noted in our dogs. The pulmonary vascular effects of MPC in humans are currently under investigation in our cardiac catheterization laboratory If pulmonary vascular resistance in humans responds to MPC as it does in dogs (vasoconstriction), important parameters such as magnitude of left-to-right shunts would be altered Thus, an increase in pulmonary vascular

resistance accompanied by a decrease in systemic vascular resistance would tend to decrease the magnitude of a left-to-right shunt at the ventricular or pulmonary arterial level. These alterations in resistance may be further enhanced in cases in which increased pulmonary blood flow is associated with increased pulmonary vasomotor reactivity.[13]

Since decisions regarding corrective cardiovascular surgery may be based upon criteria relating proportions of systemic and pulmonic blood flow, investigations in humans are indicated to evaluate the possibility that MPC might alter hemodynamics and prevent accurate assessment of a patient's usual status.

Summary

The effects of meperidine, promethazine and chlorpromazine (Demerol, Phenergan and Thorazine) were studied in the intact unanesthetized dog. MPC caused significant pulmonary vasoconstriction and systemic vasodilation in this preparation. If MPC's pharmacologic properties in humans are equivalent to those found in the present study, its suitability as a precardiac catheterization agent in some forms of cardiac disease may be open to question.

REFERENCES

1. Smith, C., Rowe, R. D., and Vlad, P.: Sedation of children for cardiac catheterization with an ataractic mixture, Canad. Anaesth. Soc. J. 5:35, 1958.
2. Goodman, L. S., and Gilman, A.: The pharmacologic basis of therapeutics, New York, 1965, The Macmillan Company, p. 267.
3. King, B. D., Elder, J. D., Jr., and Dripps, R. D.: Effect of intravenous administration of meperidine upon circulation of man and upon circulatory response to tilt, Surg. Gynec. & Obst. 94:591, 1952.
4. Goodman, L. S., and Gilman, A.: The pharmacologic basis of therapeutics, New York, 1965, The Macmillan Company, p. 171.
5. Foster, C. A., O'Mullane, E. J., Gaskell, P., and Churchill-Davidson, H. C.: Chlorpromazine: study of its action on the circulation in man, Lancet 2:614, 1954.
6. Stossel, V. K., and Sack, G.: Kreislaufuntersuchungen unter Phenothiazingaben, Psychiatrie 17:135, 1965.
7. Goldberg, S. J., Linde, L. M., Gaal, P. G., and Sachs, D.: The pulmonary and systemic hemodynamic effects produced by meperidine and hydroxyzine, J. Pharmacol. & Exper. Therap. In press.
8. Baum, D., Brown, A. C., and Church, S. C.: Sedation and O_2 consumption in cardiac catheterization, Pediatrics 39:891, 1967.
9. Israel, R., Hohn, A. R., Black, I. F. S., and Lambert, E. C.: Evaluation of sedation during cardiac catheterization of children, J. Pediat. 70:407, 1967.
10. Shackman, R., Wood-Smith, F. G., and Graber, I. G.: The "lytic cocktail": observations on surgical patients, Lancet 2:617, 1954.
11. Adams, A. K., and Parkhouse, J.: Anaesthesia for cardiac catheterization in children, Brit. J. Anaes. 32:69, 1960.
12. Rudolph, A. M., and Auld, P. A.: Physical factors affecting normal and serotonin-constricted pulmonary vessels, Am. J. Physiol. 198:864, 1960.
13. Vogel, J. H., Cameron, D., and Jamieson, G.: Chronic pharmacologic treatment of experimental hypoxic pulmonary hypertension, with observations on rate of change in pulmonary arterial pressure, Am. Heart J. 72:50, 1966.

Quantitative studies on the errors of the pulse, when used to estimate cardiac function

I Errors occurring between heart and aorta; the counter pressure difficulty

Isaac Starr M D
Philadelphia Pa

That pulse amplitude was closely related to cardiac strength has seemed self evident to most doctors all have felt the pulse diminish as death approaches. Their spokesman was Sir James Mackenzie[1] Sir Thomas Lewis[2] was more skeptical suspecting that local conditions in the vessels might distort the relationship Only one important source of error has been emphasized in the clinical literature cardiac function is underestimated when one records the pulse below an arterial obstruction. I know of no quantitative studies of the subject before those from this laboratory

Suspicions that there might be other serious errors in estimating cardiac function from the pulse were first aroused by studies of aging Pulse pressure increases as age advances but one hesitates to accept the conclusion that cardiac strength increases as one grows older apparently all other measurable bodily functions decline as age advances. A theory to explain the discrepancy was set up by Starr and Ogawa.[3]

For quantitative studies of the pulse heart relationship one needs accurate measurements of cardiac performance in systoles which differ in strength, and of the pulse waves which result from them. Such data had already been secured in experiments on fresh cadavers in which systole had been simulated at necropsy [4,5] and preliminary reports of the new quantitative studies have already been made.[6,7] The relation between cardiac function and the aortic pulse will be considered first that between aortic and peripheral pulses in a second presentation.

Methods

The apparatus and conduct of the cadaver experiments have been described in detail in previous papers.[4] After producing different diastolic pressures by femoral artery perfusion, weak and strong systoles were simulated by blows from a padded mallet, which after falling through arcs differing in size struck the pistons of syringes which injected blood or saline into the aorta and pulmonary artery During each systole the curves of cardiac ejection and of aortic and femoral blood

From the Department of Therapeutic Research, School of Medicine, University of Pennsylvania.

This work was supported by Research Grant H 11-425 from the National Heart Institute National Institutes of Health, United States Public Health Service.

Received for publication March 14 1968.

This paper and the one to follow it could be considered as Nos 14 and 15 in the Series entitled "Studies made by simulating systole at necropsy" etc.

February 1969 Vol. 77 No. 2 pp. 222-23

Table I Typical examples of pairs made to study the relation between differences of counter pressure, and differences of pulse pressure, when various aspects of cardiac function were constant, or nearly so

Subject and systole No.	*Aspect of systole used to measure cardiac strength and its magnitude*	*Mean counter pressure (mm Hg)*	*Aortic pulse pressure (mm Hg)*
R R 5	Energy used 32.8 (10^6) ergs	109	74
R R 9	Energy used 32.8 (10^6) ergs	48	34
Difference		+61	+40
E. B. 2	Stroke volume 29 c.c.	123	31
E. B 5	Stroke volume 29 c.c.	129	26
E. B 8	Stroke volume 29 c.c.	64	20
Difference of the pair (2 and 8), chosen by lot from the 3 possible pairs		+59	+11

pressures were recorded continuously by optical methods. Such experiments were conducted on subjects with varying degrees of arteriosclerosis as well as on those with normal vessels.

Part of the data obtained in these experiments has already been recorded Additional data, used in this study have been placed in Tables A and B which, too long for publication can be secured from the Library of Congress by anyone interested. A chief feature of these data is the high accuracy with which the physical aspects of cardiac function were measured some for the first time. Thus, data concerned with the energies of systole have not been provided before, cardiac work was accurately estimated by integration and velocity and acceleration of ejection could be accurately measured from the recorded curves of ejection at each instant. The method of calculating force applied has been described *

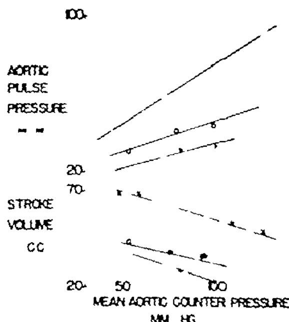
Results

Fig 1 illustrates typical data the results secured in all of the 15 systoles simulated on Subject R. R. have been arranged so that the relation between the strength of the systoles and the resulting pulse can be displayed. In this subject weak, medium and strong systoles were simulated by injections of blood propelled by the padded mallet falling through arcs which delivered 11 7 14 8, or 32 8 (10^6) ergs of energy

Inspection shows that the findings were very consistent The 3 energies introduced to simulate systole had the relation 1 1.3 and 2 8. When counter pressure was 100, the ratios of the resulting pulse pressures are 1 1 4 and 2 3 for the stroke volumes, 1 1 4 and 2 5 So when counter pressure remained the same, an increase in the energy introduced caused roughly proportional increases in both pulse pressure and stroke volume as one would expect. But the regressions drawn in Fig 1 also show that, when the energy introduced to simulate systole was kept the same an increase of aortic counter pressure was accompanied by diminished stroke volume and increased pulse pressure. This is a most interesting finding

Fig 2 shows an arrangement of the data secured on Subject R R., similar to that of Fig 1 but 4 other aspects of left ventricular performance measured beyond the syringes, are used to characterize the strength of the systole. The results are very similar to those shown in Fig 1 When as judged by any one of these criteria, the strength of the systole is the same, increase of counter pressure is accompanied by increased pulse pressure and diminished stroke volume, and vice versa.

*For supplementary Tables A and B order NAPS Document [illegible] from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, New York 10001 remitting $ [illegible] for microfiche or $1.00 for photocopies.



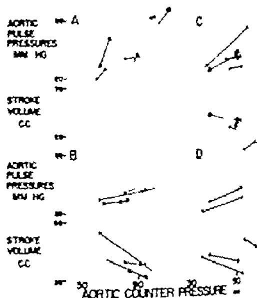


Fig. *1* Comparison bet een differences n ca diac trength measured I the d fferent mou ts of energ used to mulat tole nd the ortic pulse pressu e nd t oke *A* me resulting t different levels *of* mea aortic ou ter pressure Dat of Subject R R perfused th blood \ ndicate that the energy sed t m lat stole 52.8 circles 34.8 nd crosse 11.7 (10⁴) ergs T o poi t th the same symbol located t the same counter pres ure represent the pulse pressure nd st oke vol me produced by single s tole The l nes are the regression of the poi ts m hich the energy sed t imulate sy tole the same Note that hen counter pressu is onstant changes energ introduced lead t oughly proportional changes in pulse pressure and stroke olume But when energy introduced to simulate s tole is held onstant, increased counter pressure accompanied by increased pulse pressure nd d minished troke volume

Fig. *2* Influence of mean aortic counter pressure on aortic pulse pressure and cardiac stroke volume at various level of cardiac strength measured in di ferent ways. D ta of Subject R R perfused th blood. *A* Stroke volume is taken as the index of cardiac trength Point having identical or very simila trok volumes are given imilar symbols and connected by lines unles so close together that the slope of their regression has no significance. Reading f om left t right, in the points show as squares, the trok olumes were both 69 *c* as \ s, 53 and 5 a circled crosses, 46 nd 50 c. dots, 41 and 43 *c* a crosses 38, 36, 36 and 36 as triangle 29 nd 30 *c* Note that hen counter pressure higher the same strok volume is accompanied by higher pulse pressure *B* Stroke ork (calculated by tegration) is the index of cardiac strength. In the poi t show a \ ork la between 87 and 9 gm\l as crosses, bet een 49 6 and 52.7 as dot 46.5 and 42.3 squares 32.9 and 30 2 gm M The \ are too lo e together t determine significant lope D ta from each experimental systole appear t ice in *B* *C* and *D* to show the relations of both pulse pressure and stroke volume to counter pressure. *C* Maximum jection flow elocity is used as the index of cardiac trength I the points shown as triangles, the maximum ejection velocity was 4 nd 456 c. per second as \ s, 287 and 30 circles, 263 274 272, and 265 as dots 177 and 1 c. per second. *D* Initial force applied is used as the index of cardiac strength I the points show as \ this force was 107 (10⁵) dynes as squares, nd 85 as crosses, 61 nd 60 as dots, 36 and 3 (10⁵) dynes. Note that in ll the diagrams, when counter pressure is similar the magnitudes of pulse pressure nd stroke volume arrange themselves in accordance with the magnitude of the index of cardiac function used. But when counter pressure is increased, the same magnitude of cardiac function is accompa ied by larger pulse pressure nd smaller stroke volume, in Fig 1

To determine the size of the error caused by differences in counter pressure the following method was used because it avoids difficulties due to dependent variables in the correlations and it was easy to apply to the diverse data available First one aspect of cardiac function (e g stroke volume) was selected Second from the data of each subject pairs were sought in which this aspect was similar within narrow limits as shown in Tables I and II If this aspect was the same in 3 or more systoles as in the triple shown in Table I the pair used was chosen by lot and the remaining data dis-

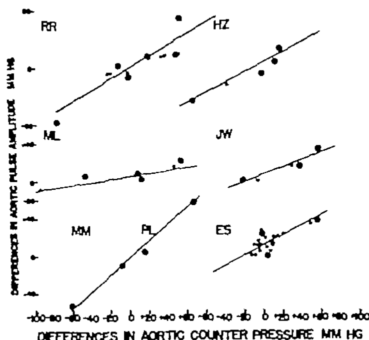


Fig 3 Relation between differences in aortic counter pressure and differences in aortic pulse pressure when there is no change in cardiac strength, as judged by the energy used to simulate systole For details of making the pairs see Table I and text.

Circled dots represent data from pairs some chosen by lot, in which no datum is used twice The regressions are calculated from these data. Smaller dots represent the extra pairs which can be set up by using certain data more than once pairs which would have been used had the lots fallen differently No best line is given for M M because certain data had to be used more than once to secure the three points shown The point of subject M M lying farthest to the right is superimposed on point of P L

The scanty data of 2 subjects, M M dots, and P L circled crosses, have been put on the same diagram The data of E B omitted for lack of space resembles those shown. In all subjects there is strong trend, increased counter pressure is accompanied by increased pulse amplitude, the scatter about the best line is small.

While it does not attain significance in all subjects because of the small numbers, when the groups are combined correlation between differences in counter pressure and differences in aortic pulse pressure is highly significant

carded. Third differences in counter pressure and pulse pressure were determined for each pair as shown in Table I Fourth, after making as many pairs as possible without using any datum twice the differences were compared by correlation techniques.

Fig 3 shows the results secured in 7 subjects when energy introduced was taken as the index of cardiac function. Obviously when the energy introduced is the same, the resulting aortic pulse pressure varies with the counter pressure in every subject This is also true when stroke volume and maximum ejection velocity were used as indices of cardiac strength, as are shown in Fig 4

Table II gives the results of the statistical analysis of data secured when 5 aspects of cardiac performance were studied in 6 subjects perfused with blood The size of the counter pressure error can be calculated from the slope of the regressions There is a sharp division in the results which is of great interest.

When energy stroke volume or ejection velocity are used to make pairs in which cardiac strength is the same correlations between changes of counter pressure and changes of pulse amplitude are highly significant and the slopes of the regressions indicate that an increment of mean counter pressure of 10 mm Hg would be automatically accompanied by an increment of pulse pressure of about 5 mm. Hg though cardiac function was unchanged

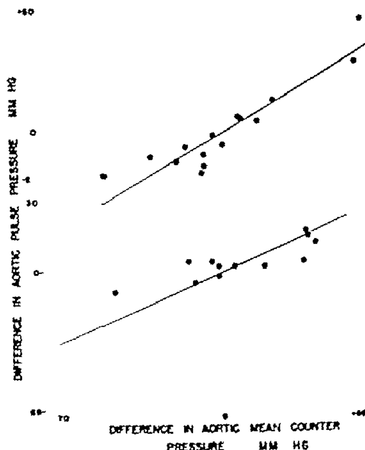


Fig. 4 R lations between differences in mean aortic ounter pressure and aortic pulse pressure hen cardiac function i the same. Data from subjects perfused with blood, pairs made as described in text. Y data is used twice.
Top. troke olume is used to indicate that cardiac function was imilar in each pair. The perfusion ... are in Table II.
Bottom maximum ejection velocit as sed for this purpose.

But when cardiac strength was judged equal by aspects of cardiac performance in which counter pressure is a factor such as work, there was no significant correlation between counter pressure and pulse pressure in the pairs and the slope of the regression is not significantly different from zero in our studies.

The experiments in which water was injected to simulate systole were certainly less physiological than when blood was used but the results are confirmatory. When the 2 groups of data are combined the correlations of items 1, 2 and 3 (Table II) remain highly significant; those of items 4 and 5 remain close to zero.

The magnitude of other errors can be studied by eliminating the counter pressure difficulty by pairing it out. For reasons given at length in Part II of this series maximum flow velocity was selected as the most suitable measure of cardiac function. Using a method similar to that described above pairs were arranged in which the counter pressure was equal within limits of 5 mm Hg; differences in aortic pulse pressure and maximum flow velocity were determined in each. The correlation between these 2 differences was extraordinarily good. In 16 pairs secured in subjects perfused with blood $r = 0.93$; when 6 pairs secured in subjects perfused with water were added $r = 0.90$. In the 22 pairs in 6 subjects the estimating equation is

Differences in maximum ejection velocity c.c. per sec. = −6 + 7.7 (differences in aortic pulse pressure mm. Hg) (1

Table II Relation between differences in counter pressure and changes in aortic pulse pressure when various aspects of cardiac function are unchanged

Item	Aspect selected to show that cardiac function was unchanged	Limits of difference allowed in pairing	Data from experiments in which injections of blood were used to simulate systole				Data from experiments in which injections of water were used to simulate systole combined with those in which blood was used			
			No. of pairs	Correlation coefficient	Sig†	Counter pressure error* (mm. Hg)	No. of pairs	Correlation coefficient	Sig†	Counter pressure error* (mm. Hg)
1	Energy used to simulate systole	1 (10⁴) erg	22	0 82	yes	5 2	33	0 82	yes	7 3
2	Stroke volume	5 c	16	0 91	yes	5 8	26	0 78	yes	3 9
3	Maximum ejection velocity	40 c.c./sec	18	0 82	yes	4 3	28	0 72	yes	2 9
4	Work	10 gmm	15	0 32	no	1 3 ?	23	0 07	no	1 0
5	Maximum ejection velocity × mean aortic BP	10 (sec × mm Hg + 100)	13	0 25	no	2 5 ?	19	0 12	no	1 0 ?

*Counter pressure error is defined as the increment of aortic pulse pressure (mm. Hg) which accompanies 10 mm. Hg increment of mean aortic counter pressure when cardiac function is unchanged
†Significance for P = 0 05

The standard deviation about the regression is 74 c.c. per second 25 per cent of the average value.

One can study the errors remaining after the elimination of those due to counter pressure in another way We have 17 systoles in 5 subjects perfused with blood in which counter pressure was normal that is, ranging from 90 to 110 mm Hg it varied so little that this error must have been small or absent In these data, there is highly significant correlation between aortic pulse pressure and maximum ejection velocity $r = 0.81$ and the standard deviation about the regression is 54 6 c.c per second, 18 per cent of the mean maximum ejection velocity a value for the remaining error a little smaller than that secured by pairing

In contrast if one ignores the height of counter pressure and studies the correlation between aortic pulse amplitude and maximum ejection velocity in all the 52 systoles performed in 6 subjects perfused with blood one finds that r now 0.42 This is still highly significant but the standard deviation about the regression has increased to 176 c.c. per second indicating about twice the scatter found when the counter pressure error was eliminated

Obviously one could make only a very poor estimate of maximum ejection velocity from *aortic* pulse amplitude without correcting for the counter pressure error whenever counter pressure is abnormal But even after such correction, considerable errors remain. Estimates of maximum ejection velocity made independently from our records by 2 observers, had an average difference of 6 per cent of the mean value, so such inherent errors will account for a certain part of the remaining error but not for all of it.

Discussion

In these experiments, the heart action was mimicked by an energy source and, as far as I know this has not been done in any other model of the circulation pressure sources and flow sources have been commonly used. Knowledge of the energy used provides an important indication of *total* cardiac" performance in a way that the commonly used measurements of flow and pressure do not.

But before one draws conclusions from the magnitudes of the energies used in our studies a difficulty must be discussed. Despite scrupulous care to keep the syringes clean and well oiled, as in all piston systems over 80 per cent of the energy introduced was lost as friction in our experiments. Also part of the energy introduced went into the pulmonary circulation. If the energy lost was always a constant part of the whole there would be no difficulty but this is not to be assumed. Indeed, in our experiments when energy introduced was kept the same the cardiac work performed increased a little as counter pressure increased. This finding I explain as follows: in systoles powered by the same energy the higher the counter pressure the less the movement of the piston so friction was less when counter pressure was high and more of the energy introduced survived to do work beyond the pistons. Differences in friction will also explain the finding (Figs. 1 and 2) that when counter pressure was constant stroke volume and pulse pressure increased somewhat less than the increments of energy used to produce them. But our chief findings cannot be due to differences in friction for when this error is avoided altogether by using aspects of cardiac function measured beyond the syringes, such as stroke volume, the findings remain the same. Counter pressure is obviously a factor of great importance in the relation of many aspects of cardiac function to pulse amplitude.

To many this finding will come as a surprise. One would expect that pulse amplitude would depend directly on the volume ejected but in these experiments it does not do so. The explanation is in the nonlinearity of the physiological situation in the vessels: when counter pressure is raised pulse wave velocity is found to be much increased in our experiments and distensibility has diminished. So when counter pressure is high a smaller amount injected causes a greater rise in pressure.

Analogous results have been found in some models, but not in all. In Robinson's[8] electrical circulation analogue the pressure encountered by the discharging ventricle dominated the results; when arterial pressure increased stroke volume decreased as in our studies. In Beneken's mathematical study when peripheral resistance was raised pulse pressure increased and stroke volume diminished as in our experiments. However Noordergraaf's electrical model has been built with a linear situation in the vessels and when tested in it this phenomenon is absent.

In dogs Warner[1] secured evidence that the peripheral resistance faced by the ventricle was a major determinant of stroke volume. Scher and associates[1] found aortic pressure to be one of 3 important determinants of stroke volume. Peterson,[11] who injected similar jets of fluid into the aortas of dogs found that the amplitude of the resulting pressure waves increased as the pre-existing aortic pressure increased. Such findings, so similar to ours, encourage one to believe that the results found in our cadavers have a wide applicability.

We have not been able to demonstrate that the pathological state of the vessels has a significant effect on our results but it should be noted that in Fig. 3 the regressions of those with most normal vessels, ML and MM, appear flatter than the other regressions and this is consistent with the conceptions expressed above.

Our findings introduce a complexity into the heart pulse relationship that can be best explained by a consideration of the results recorded in the lower half of Fig. 1 for the coordinates of this part of that figure are the 2 terms of the right side of the equation long used for the approximate estimation of cardiac work.

Cardiac work = stroke volume × mean pressure (1)

The results recorded in Fig. 1 show clearly that for systoles powered by the same energy as mean counter pressure increases, pulse amplitude increases but stroke volume diminishes. We interpret this finding as follows: the energy supplied by the cardiac contraction on reaching the aorta, is divided between potential and kinetic energies; the pulse amplitude is related to the former and is independent of the latter. So pulse amplitude reflects only a part of the cardiac energy and this part bears no fixed relation to the whole. The proportion between the 2 kinds of energy resulting from the cardiac contraction varies with the counter pressure because counter pressure impedes the flow of blood

and the higher the counter pressure the more energy is required to overcome the impedance, and less energy remains to initiate flow

Practical considerations also stem from our data. The doctor seeking knowledge of cardiac flow functions such as stroke volume or ejection velocity from observations of the peripheral pulse would greatly improve his estimate by a correction for differences in counter pressure of the form

$$\text{Stroke volume} = b \frac{(\text{pulse pressure})}{(\text{mean counter pressure})} + \quad (3)$$

As the regressions shown in Figs. 3 and 4 pass so close to the origin, *a* will be small. This formulation can also be used to explain the striking discrepancy in our data the strong correlations of items 1 2 and 3 in Table II and the lack of correlation of items 4 and 5 For if one multiplies both sides of equation (3) by mean counter pressure and substitutes in equation (2) then

$$\text{Stroke work} = b\,(\text{pulse pressure}) + (\text{counter pressure}) \quad (4)$$

Since *a* is so small when one makes an estimate of stroke work from the pulse the counter pressure correction is probably negligible. This reasoning is in complete accord with a previous finding that peripheral pulse amplitude is far more closely related to stroke work than to stroke volume.

Conclusion

Results secured when systole was simulated at necropsy permit a comparison between differences of cardiac strength and the resulting aortic pulse amplitude.

When counter pressure is constant, the magnitudes of many aspects of cardiac strength are roughly proportional to the amplitudes of the aortic pulse waves which result from the systoles. Unfortunately differences in aortic counter pressure may seriously distort such heart-pulse relationships.

If cardiac strength is defined by flow measurements such as stroke volume or maximum ejection velocity a change of mean aortic counter pressure of 10 mm Hg results in an automatic increase of about 3 mm Hg in pulse pressure, when cardiac performance is unchanged So the doctor attempting to judge such aspects of cardiac function from pulse amplitude will seriously overestimate them in hypertension and underestimate them in shock unless a correction is made for the counter pressure error

However when cardiac strength is defined by work or by any aspect of cardiac performance in which counter pressure is already a factor the needed correction has, so to speak already been inserted and the remaining counter pressure error is so small that it is probably negligible.

But even after such correction a certain error remains, too large to be attributed to the inherent error of the experiment. Nevertheless, when counter pressure is normal or after the disturbing effects of counter pressure differences have been eliminated one can properly make a rough estimate of certain aspects of cardiac performance from the aortic pulse.

I am indebted t Dr A. Noordergraaf for several important suggestions for improving the physical aspects of the discussion in this and the following paper

REFERENCES

1 MacKenzie, J The study of the pulse, Young J Pentland, Edinburgh and London, 1902
2 Lewis, T Diseases of the heart, London, 1933 The Macmillan Company
3 Starr I nd Ogawa, S O the aging of the heart, why is t so much more conspicuous the ballistocardiogram than in the pulse Am J M Sc. 241:399 1961
4 Starr I Schnabel, T G and Mayock, R. L Studies made by sim lating systole t necropsy II Experiments on the relation of cardiac nd peripheral factors to the genesis of the pulse w ve and the ballistocardiogram, Circulation 8:44 1953.
5. Starr I and Schnabel, T G. Studies made by sim lating systole t necropsy III On the genesis of the systolic waves of the ballistocardiogram J Clin. Invest. 33 10 1965
6. Starr I Influence of cou ter pressure on pulse amplitude. Abstracts of papers presented at XXIII International Congress of Physiological Sciences, Tokyo, Japa 1965 p. 144
7 Starr I Effect of differences in cardiac f nc tion on pulse transmission Fed. Proc. 25:470 1966.
8. Starr I Askovitz, S I Feder W and Schild, A. Studies made by simulating systole t necropsy VII Clinical methods for estimating the work of the left ventricle, Circulation 12 1005, 1955
9 Starr I Studies made by simulating systole at necropsy XII The estimation of the initial

cardiac forces from the ballistocardiogram. Circulation 20:74, 1959.
10. Robinson, D. A.: Ventricular dynamics and the cardio-representation problem. Circulatory analogue computers, North Holland, Amsterdam, 1963.
11. Beneken, J. E. W.: A mathematical approach to cardiovascular function. Ph.D. Thesis, University of Utrecht, 1965.
12. Starr, I., and Noordergraaf, A.: Ballistocardiography in cardiovascular research. Physical aspects of the circulation in health and disease. North Holland, Amsterdam, Philadelphia, 1967, J. B. Lippincott Company.
13. Warner, H. R.: In Handbook of physiology. Am. Physiol. Soc., Washington, D. C. 196 Chap. 50, section 2, vol. III.
14. Scher, A. M., Young, A., and Kehl, T.: Regulation of stroke volume in resting unanesthetized dog. Information Exchange Group No. 1, Scient. Memo 66, 1966.
15. Peterson, L. H.: Dynamics of pulsatile blood flow. Circulation Res. 2:127, 1954.
16. Starr, I.: Studies made by simulating systole at necropsy. XI. On the higher dynamic functions of the heart and their reflections in the pulse wave. Circulation 17:589, 1958.
17. Starr, I.: Studies made by simulating systole at necropsy. VIII. Significance of the pulse pressure. Circulation 14:1117, 1956.

Quantitative studies on the errors of the pulse when used to estimate cardiac function

II. Errors occurring during pulse transmission with an estimate of the total error

Isaac Starr, M.D.
Philadelphia, Pa.

That the pulse wave becomes taller and steeper as it travels down the arteries has been known for many years. Average normal increments are given in the literature, but the search made before beginning this investigation disclosed no data whatever on the variability of the increment, and the question whether changes in cardiac function or differences in arterial properties affected the gain in amplitude did not appear to have been raised.

In the series of cadaver experiments performed in this laboratory, simultaneous records of the same pulse wave were made by 2 optical manometers, one recording from the ascending aorta, and the other from the femoral artery. These pulse waves had their origin in simulated systoles whose characteristics, known exactly, mimicked normal and abnormal cardiac contractions, both in subjects with normal vessels and in those with varying degrees of arteriosclerosis. These data have been analyzed to define the errors to which a doctor attempting to judge cardiac function from the peripheral pulse would be subject. We have also sought to discover physiological factors responsible for the marked variability of the changes found in the pulse wave as it traveled to the periphery in our subjects.

Methods

The conduct of the cadaver experiments has been briefly described in the previous report where references to detailed descriptions of technique and subjects have been given.

Results

Table I shows the means of the increments and decrements of pulse amplitude as the wave traveled to the periphery and the standard deviations about these means. The changes in pulse amplitude ranged from +23 mm. Hg to −16 mm. Hg in subjects perfused with blood; expressed as per cent of the aortic pulse pressure, they ranged from +53 to −26 per cent. In the systoles simulated by injections of water the range of the scatter was even larger, from +53 to −11 mm. Hg, and from +100 to −55 per cent.

The data secured in each systole were arranged in order of the magnitude of the pulse increment, to permit easy comparison

Department of Therapeutic Research, School of Medicine, University of Pennsylvania.
This work was supported by Research Grant No. H 420 from the National Heart Institute, National Institutes of Health, United States Public Health Service.
Received for publication March 4, [illegible].

Table I Variability of change in amplitude as the pulse travels from aorta to femoral artery in cadaver experiments

Subject	No. of systoles	Perfusion blood or water	Mean change in pulse amplitude		Standard deviation about the mean	
			mm Hg	%	mm Hg	%
M L	10	B	+ 6 9	19 8	3 7	9 9
J W	9	B	+ 4 2	11 3	4 9	1 5
H Z	12	B	+ 5 1	7 6	6 8	9 8
M M	5	B	+ 6 4	36 8	3 3	19 4
R R	15	B	+ 3 2	12 1	6 8	6 8
P L	4	B	+13 2	28	8 3	30 4
B	36	B	+ 5 6	16 1	6 4	15 5
E S	12	W	+13 3	15 0	17 2	19 3
E B	13	W	+ 3 3	16 1	7 8	34 4
P L	5	W	+17 2	20 6	5 7	8 8
B	30	W	+ 9 6	16 4	12 9	23 8

with the magnitude of cardiac and peripheral factors present Cardiac factors available for comparison included the energy used to simulate systole stroke volume stroke work average and maximum ejection velocity and initial acceleration and the peripheral factors included the amount of arteriosclerosis present as rated at the necropsy the counter pressure resistance and the vascular distensibility as judged by pulse wave velocity The pulse waves were characterized by their initial amplitudes, and the slopes of the wave's front as well as by the changes in amplitude as they traveled peripherally Much too long for publication Table A and the supplementary Table B can be secured from the Library of Congress by anyone interested

These ample data were carefully searched for significant correlations between differences in pulse transmission and differences in cardiac performance, or of vascular properties and structure the very few found will be discussed below

Discussion

The chief feature of our results is the large scatter of the data shown in Table I The gain in amplitude as the pulse travels is very variable There is unexpected variation both between subjects and within individuals.

In our cadavers the average gain in amplitude as the pulse wave travels to the periphery (Table I) is significantly correlated with the subject's age. When gain is expressed in per cent $r = -0.77$ The regression is

$$\text{Pulse gain in per cent} = 48 - 0.5 \text{ age} \qquad (1)$$

To make a prediction for the gain at 20 years of age from this regression requires a long extrapolation for our youngest subject was 43 but it gives a value of 39 per cent O Rourke and his collegues[3] found an average gain of 41 per cent in their subjects of this age But our data indicate an average increment of 23 per cent at the age of 50 so we expect a larger average gain than the 5 per cent found by these authors in their few subjects of that age. But surely differences in age and in the arteriosclerotic changes which accompanied it in our subjects, are important factors in the scatter between subjects shown in Table I.

But there is also marked scatter of the data when systoles of different kinds send pulse waves down the vessels of the same subject at differing counter pressures, as is shown by the large standard deviations found for each subject (Table I) The recent work of Rowell and his associates[4]

*For supplementary Tables A and B, order NAPS Document 00219 from ASIS National Auxiliary Publications Service c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, New York 1000 1 remitting $1.00 for microfiche or $3.00 for photocopies.

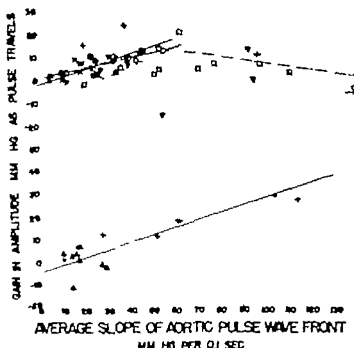


Fig 1 Relation of change in amplitude as the pulse travels from aorta to femoral artery and the average slope of the aortic pulse wave front Upper data from systoles simulated by injections of blood. Data of subject P.L crosses M.L., circles J.W. X H.Z squares R.R triangles, point down M.M dotted circles Solid line regression of the data of J.W broken line of M.L. dashed line of H.Z dashed and dotted line, regression of all waves with slope over 60 mm. Hg per 0.1 sec. Lower data from systoles simulated by injections of water Data of subject E.S., dots P.L crosses, E.B triangles, point up The line is the regression of all the data, the best estimates of pulse gain from pulse slope Note the strong correlation between pulse slope and gain of amplitude when systole is simulated by water This relation does not hold for the data of the whole group perfused with *blood*, but it is significant in 2 individuals whose pulse slope never exceeded 50 mm. Hg per 0.1 sec., and just misses significance in one other But, when blood is injected, as the wave front becomes steeper the scatter increases and finally the trend is reversed, the correlation of all the points in which X > 60 mm. Hg per 0.1 sec. is negative and this is significant. The arrow indicates that this square should be placed further to the right, at X = 174

demonstrates similar changes in living individuals, for when their subjects exercised the gain in amplitude as the pulse traveled was twice that when they were at rest Our studies do not provide a complete explanation of these differences in individuals, but several possible factors deserve discussion

As is shown in Fig 1 when systole was simulated by injections of water the gain in amplitude as the pulse travels is clearly related to the average slope of the aortic pulse wave front This correlation is very strong for of the 3 subjects for E.S. = 0.92 for P.L., r = 0.93 Similar data secured in the third subject E.B show no significant correlation but the range was too restricted to demonstrate such a relation, if it existed When all these data are combined the correlation in the 30 systoles is still very strong = 0.76 and P far exceeds 0.01 Such a finding suggests that both cardiac and vascular components may play a part in the gain in amplitude for the slope of the pulse wave front increases both as the initial acceleration of ejection increases and with increasing initial resistance.

Unhappily this attractive theory is not supported by the data secured when systole was simulated with blood when viewed in its entirety In the 59 systoles" made by injecting blood correlation between aortic pulse wave slope and gain in amplitude is close to zero However in 2 of our subjects, M.L. and J.W., the relation so prominent in the water experiments is significant,

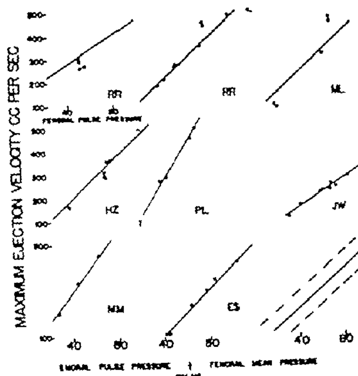


Fig 2 Studies of one abil ty to measure cardiac strength (judged by maximum flow elocity) from the peripheral pulse mpl tude nd from the quotient pulse amplitude ÷ mean blood pressure Judged by the data secured in the last 7 cadavers tested E.S. was perfused with water the other subjects with blood. Upper left, peripheral pulse amplitude is compared with cardiac trength in subject R R Not the comparatively poor relationship (= 0.61). Upper middle the quotient, peripheral pulse amplitude ÷ peripheral mean pressure X 100, is ompared w th cardiac strength in R R Note the great improvement in the correlation (= 0.80) If the off point is omitted (as w done in several previous papers because of evidence of a technical difficulty) = 0.93 Upper right, middle ow lower left, and middle similar data on other subjects. Note the strong relationships for M L., = 0.75 for H Z. = 0.92 for P L. = 0.99 for J W = 0.86 for M.M = 0.79 for E.S. = 0.92. All are highly significa t. Lower right, the regression of ll the data secured in subjects perfused with blood (= 38) ith the tandard deviation about it = 0.75 nd sig ific nce of this correlation greatly exceeds P = 0.01

$r = 0.9?$ and 0.72 respectively In both of these subjects, although the maximum energy used to simulate systole was as great as in the other experiments, the slope of the resulting pulse wave front was never very steep the maximum being 56 mm. Hg $\frac{\text{sec}}{10}$ In other subjects when the slope of the wave front was a little steeper than this marked instabil ty appeared and when still steeper the slope of the regression turned downward (Fig 1)

In one subject I L. systoles were simulated with both blood and water The range of energy used to simulate systole was the same for both series of injections but the resulting waves behaved altogether differently In 5 systoles, when water was injected the gain in amplitude as the pulse traveled was strongly correlated with the slope of the pulse wave front $r = 0.93$ in 5 others, when blood was used there was no correlation $r = -0.23$ So the fact that injections of blood and water behave so differently in our experiments cannot be attributed to differences in the subject's vessels or in the strength of the systoles it must be due to the very different physical properties of the 2 fluids. Unhappily it is the results secured when blood is used that are the more unpredictable in our data.

Despite this meager support from our own data the recent findings in man support the theory for after the heart is stimulated by exercise the gain in pulse transmission doubles[4] and young people whose hearts are likely to beat very strongly have

a far larger pulse transmission gain than do people of 50 years of age when the heart beats less strongly

But evidently this theory affords no complete explanation and the situation is far more complicated and unstable than has been believed. Obviously the cause of the variability should be sought in analysis of the frequency components and reflection characteristics of pulse waves[7] rather than in correlation with the simple physiological differences found in our data. This view is consistent with the results now before us, for the magnitude of the various frequency components of any pulse wave is determined by the magnitude and arrangement of the forces of the cardiac contraction and when these were altered experimentally differences in pulse transmission would be expected. Further study in this direction is beyond the scope of this investigation, for one sees no prospect of securing a simple means of correcting for the transmission errors by Fourier analysis.

Nevertheless, our data enable one to estimate the size of the errors to which the doctor would be subject, when he feels or records the peripheral pulse, or determines the peripheral pulse pressure, in order to learn about the strength of the heart in patients with cardiac or vascular disease

Studies to define the total error of the pulse Several reasons impelled us to choose the maximum flow velocity of ejection as the best single quantitative measure of cardiac strength to compare with peripheral pulse amplitude first, measured beyond the syringes it avoids complications due to differences in piston friction in our experiments second there is increasing evidence that important clinical information is contained in the acceleration of ejected blood[4] and the maximum flow velocity is the time integral of the accelerations which preceded it third there is reason to believe that the exact relation between maximum flow velocity and pulse pressure can be expressed by a simple arithmetical equation whereas certain other relations such as that between pulse pressure and stroke volume would require a set of differential equations for their exact expression fourth, maximum flow velocity could be accurately measured in our records.

In addition the time correspondence between maximum velocity of ejection and the peak of pulse amplitude is excellent both in our cadaver studies and also in dogs, and this is not true for aspects of cardiac function such as stroke volume or stroke work. Indeed simultaneous records made both in our studies and in dogs show that the pulse peak occurs, and so pulse amplitude is determined when less than half the stroke volume has been injected In dogs 50 per cent of pulse amplitude may be attained when only 3 per cent of the stroke volume has entered the aorta.

So methods seeking to relate stroke volume or stroke work to pulse amplitude must assume that the large fraction of the stroke volume ejected after pulse amplitude is determined bears a constant relationship to that part ejected before. When abnormal cardiac function is simulated in our cadaver experiments, this assumption does not hold and we believe it would not hold when cardiac function becomes abnormal during life.

The study described in the preceding paper and illustrated in part in Fig 2 indicates that the ratio *aortic* pulse pressure ÷ *aortic* mean pressure provides a better estimate of maximal ejection velocity than *aortic* pulse amplitude alone Many years ago a similar ratio was used to improve estimates of cardiac output from the peripheral pulse by Liljestrand and Zander

From data of all 59 systoles simulated by injections of blood in 6 subjects, the estimating equation is

$$\text{Maximum ejection velocity c.c./sec} = 403 \; \frac{\text{femoral pulse pressure}}{\text{femoral mean pressure}} + 59 \quad (2)$$

The magnitude of the errors of this estimate is given by the standard deviation about the regression, which is 74 c.c. per second 25 per cent of the mean value of maximum ejection velocity in our experiments. So the errors are larger than has been realized.

An interesting aspect of the general problem can also be presented here If one multiplies both sides of equation (2) by femoral mean pressure one removes the correction in the denominator on the right side and finds on the left a most interesting expression which can be thought of as

indicating the heart s effort.[8] Written in its approximate form it resembles the approximate form of the cardiac work equation except that the term concerned with flow is the first time derivative of that used to estimate Newtonian work. This unfamiliar aspect of cardiac function is directly related to pulse amplitude *itself* and it is the source of the doctor s information when he studies pulse amplitude alone When equation (2) is thus rewritten the errors concerned with the doctor s estimate of cardiac function from *pulse* amplitude alone are the same as those mentioned above

In the clinic the doctor depending on the pulse for *his* knowledge of cardiac well being must face another difficulty for the evidence is overwhelming that when the heart begins to weaken the pressure in the circulation is maintained at the expense of flow For this reason pulse amplitude cannot be expected to carry important information about the early changes of cardiac function in disease

But if *pulse* amplitude or the ratio, pulse amplitude ÷ mean pressure is less than ½ the normal mean the doctor has significant evidence that the heart is abnormal Which of the 2 ways of looking at cardiac function is the more valuable can be decided only on the basis of experience

Conclusion

When cardiac strength is estimated from peripheral pulse pressure or by palpation of the peripheral pulse the errors involved are much larger than is commonly believed

REFERENCES

1 Handbook of circulation, Philadelphia [
London, 1959 W B. Saunders Compan
2. Starr I Effect of differences in cardiac fu
t on on pulse transmission, Fed. Proc. 25:
1966.
3 Starr I Quantitative studies on the errors of th
pulse when used t estimate cardiac functio
I Errors occurring between heart and ar..
the con ter pressure difficulty Am. Heart J
77:222 1969
4 Rowell, L. B. Brengelmann, G. L., Blackm
J R Bruc R. A., and Murray J A. Di
parities between aortic and peripheral pul
pressures induced by upright exercise and va
motor changes in man, Circulation 37:9
1968.
5 O Rourke, M F Blazek, J N Morreels, C.L
J Krovetz, L. J and Milnor W R. Effe
of age and arterial disease on pressure tra
transmission along the human aorta, Fed Pro
27:230 1968.
6. Starr I and Noordergraaf A. Ballistocardiog
raphy in cardiovascular research. Physical a
pect of the circ lation in health and disea
North Holland, Amsterdam, Philadelphia, 196
J B Lippincott Company
7 M Donald, Donald Blood flow in arter
Baltimore 1960, The Williams & Wilkins Co
pany
8. Starr I Studies made by simulating systole
necropsy XI On the higher dynamic functi
of the heart and their reflections in the pul
Circulation 1 :589 1955.
9 Noble M I M Gabe, I T Trenchard, I
nd Guz, A Blood pressure and flow in th
aorta of conscious dogs, Cardiovas. Res. 1
1967
10 Liljestrand, G and Zander E. Vergleichend
Bestimmungen des Minuten volumens d
Herzens beim Menschen mittels der Sti
oxydul methode und durch Blutdruckmessung
Ztschr exper Med. 59 105, 1928.

Prophylaxis versus treatment of acetylstrophanthidin intoxication

Howard J. Zeft, M.D.
*Robert E. Whalen, M.D.***
James J. Morris, Jr., M.D.
*Nicholas J. Rummo, A.B.****
*Henry D. McIntosh, M.D.******
Durham, N. C.

Diphenylhydantoin (Dilantin) and beta-adrenergic blocking agents have become valuable adjuncts in the treatment of digitalis-induced cardiac arrhythmias.[1-4] Recent studies in anesthetized dogs have indicated that the prophylactic administration of diphenylhydantoin increased the toxic to therapeutic ratio of digitalis. Some investigators have reported that pretreatment of anesthetized animals with beta sympathetic blocking agents has produced protection against digitalis-induced arrhythmias, while others have noted *no* prophylactic effects. In addition, the mechanism of action of beta blocking agents in digitalis arrhythmias has been considered to be related to their "quinidine-like" properties and not to beta sympathetic blockade. A recently introduced beta blocking agent, 4-(2-isopropyl-amino-1 hydroxyethyl) methanesulfonanilide (MJ 1999) has been reported to be devoid of quinidine-like properties and to be effective selectively against catecholamine-induced arrhythmias but not against those precipitated by ouabain.

The purpose of the present study was to evaluate the use of diphenylhydantoin and 2 beta-adrenergic blocking agents in the prevention and treatment of acetylstrophanthidin induced cardiac arrhythmias in the conscious animal. One of these beta blocking agents, propranolol, is reported to have a prominent quinidine-like effect and the other, MJ 1999, is supposedly devoid of this property.[18] In the present

From the Cardiovascular Laboratory, Department of Medicine, Duke University Medical Center, Durham, N. C.
These studies were supported in part by Research Grants HE-1809, HE-5389, HE-07303 [illegible] the National Heart Institute, United States Public Health Service and Grants-in-aid from the John A. Hartford Foundation, Inc. and the Parke, Davis and Company.
Presented before the fortieth annual American Heart Association meetings, October, 1967, San Francisco, Calif.
Received for publication March 21, 1968.

*Work completed during the tenure of Dr. Zeft's support as Postdoctoral Research Fellow of the National Heart Institute, NIH, United States Public Health Service. Postdoctoral Research Fellow, Cardiovascular Laboratory, Department of Medicine, Duke University Medical Center, Durham, N. C.

**Associate Professor of Medicine, Department of Medicine, Duke University Medical Center, Durham, N. C.

***Assistant Professor of Medicine, Director, Cardiovascular Laboratory, Department of Medicine, Duke University Medical Center, Durham, N. C.

****Third year medical student, Duke University School of Medicine, Durham, N. C.

*****Professor of Medicine, Chief, Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, N. C.

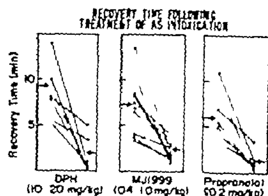


Fig 1 The effect of diphenylhydantoin (DPH), MJ 1999 and propranolol on the treatment of acetylstrophanthidin-induced ventricular tachycardia in the awake pig. The ordinate indicates recovery time in minutes from ventricular tachycardia to sinus rhythm. At the bottom of each panel the dosage of the drug administered to each set of each case is shown. The points on the left of each panel represent control values and those on the right values after drug treatment. Each line connects control and treatment data for a given animal. Arrows represent mean for control and treatment studies.

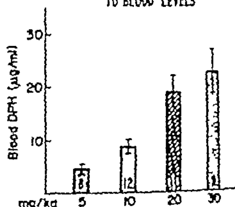


Fig 2 The relationship of diphenylhydantoin (DPH) dose to diphenylhydantoin blood levels. Blood concentrations were measured on venous blood samples obtained during acetylstrophanthidin administration. Each bar represents mean ± S.E. value. The numbers at the bottom of each bar indicate the number of determinations from which mean values were obtained.

study an attempt was made to answer the important question as to whether these antiarrhythmic agents will effectively increase the toxic to therapeutic ratio of acetylstrophanthidin in an awake animal. Repetitive studies were performed in conscious ambulatory farm pigs, whose reflexes were presumably intact.

Method of acetylstrophanthidin testing

Awake ambulatory farm pigs weighing 10 to 15 kilograms served as experimental animals. Acetylstrophanthidin was administered intravenously through an indwelling No. 9 Bardick catheter which had been previously inserted into the superior vena cava via the external jugular vein. Electrocardiograms were monitored continuously by radiotelemetry.

An initial dose of 0.5 mg. of acetylstrophanthidin was followed by repeated injections of 0.1 mg. at 1 minute intervals until the end point of ventricular tachycardia lasting at least 15 seconds was reached.

Acetylstrophanthidin in the powdered form was diluted in physiologic saline in a concentration of 0.1 mg. per milliliter. Acetylstrophanthidin was generously supplied by Eli Lilly and Company, Indianapolis, Ind.

Other electrocardiographic signs of digitalis toxicity, such as premature beats, bigeminal rhythm, or grades of A-V block, were disregarded until the end point was attained. In many cases, actual ventricular tachycardia could not be distinguished from supraventricular or junctional tachycardia with aberrant ventricular conduction, but the abrupt change from sinus rhythm to tachycardia was easily discernible. Previous studies in this laboratory have shown that, in a given animal, this test is reproducible in terms of the amount of acetylstrophanthidin necessary to produce tachycardia and the time interval from the onset of tachycardia to the return to sinus rhythm (recovery time).[11] Morris and associates performed 86 base line acetylstrophanthidin tolerance tests in farm pigs with an average intoxicating dose of 2.18 ± 0.25 mg. (1 S.D.). These investigators noted that 95 per cent of repeated tests on control animals fell within ±0.5 mg. (2 S.D.) of initial base-line values.

Duplicate control tests to determine the intoxicating dose of acetylstrophanthidin and the recovery time after intoxication were performed on each animal undergoing pharmacologic testing with diphenylhydantoin or beta adrenergic blocking drugs.

Thus, each animal served as his own control for the statistical analyses.

Treatment studies

Methods. A total of 31 animals underwent duplicate control tests with acetylstrophanthidin on consecutive days, thus establishing the average intoxicating dose and recovery time in each animal. For the treatment studies, acetylstrophanthidin intoxication was induced and either diphenylhydantoin, MJ 1999, or propranolol were administered intravenously at the onset of ventricular tachycardia. Nine animals were treated with diphenylhydantoin* (10 mg. per kilogram per minute given over 1 or 2 minutes), 12 with MJ 1999† (6 animals at a dose of 0.4 and 6 animals at a dose of 1.0 mg. per kilogram), and 10 with propranolol† (0.2 mg. per kilogram). Recovery time (from the onset of tachycardia to sinus rhythm) was recorded for all of the treatment studies and compared to control values in a given animal.

Results. The intravenous administration of diphenylhydantoin, MJ 1999, and propranolol after the induction of tachycardia significantly shortened recovery time. Fig. 1 illustrates the effect of each of these agents in decreasing the duration of acetylstrophanthidin induced tachycardia. Mean recovery times decreased from 9.3 to 2.0 minutes in 7 of 9 animals treated with diphenylhydantoin ($p < 0.01$), from 7.3 to 2.5 minutes in 10 of 12 animals treated with MJ 1999 ($p < 0.01$), and from 6.1 to 1.4 minutes in 8 of 10 animals treated with propranolol ($p < 0.01$). Two animals from each of the drug treatment groups died with progression of ventricular tachycardia to ventricular fibrillation.

Pretreatment studies ("prophylaxis")

Methods.

DIPHENYLHYDANTOIN. Initially, the average intoxicating dose of acetylstrophanthidin was established from 2 tests performed on separate days, in each of 22 pigs. On subsequent days, a total of 30 acetylstrophanthidin tolerance tests were performed in the 22 pigs 15 minutes after diphenylhydantoin had been injected intravenously. Ten studies each were performed at dose levels of 5 and 10 mg. per kilogram and 5 studies each after diphenylhydantoin doses of 20 and 30 mg. per kilogram. Venous blood samples for the determination of diphenylhydantoin blood concentrations were drawn immediately prior to acetylstrophanthidin testing and at the end point of tachycardia. Blood diphenylhydantoin concentrations were measured by the method of Plaa and Hine.[12] The efficacy of diphenylhydantoin pretreatment was evaluated by (1) comparing acetylstrophanthidin intoxicating doses in control studies with those noted after diphenylhydantoin pretreatment, (2) comparing recovery time from tachycardia to sinus rhythm in control studies versus that after diphenylhydantoin pretreatment, and (3) comparing the mortality rate from control tests with that observed after pretreatment with diphenylhydantoin.

BETA ADRENERGIC BLOCKADE. After duplicate control studies, a total of 23 animals were pretreated with either MJ 1999 or propranolol prior to acetylstrophanthidin testing. MJ 1999 was injected intravenously over 1 minute, 5 minutes prior to acetylstrophanthidin administration. Eleven studies were performed after MJ 1999 doses of 0.1 mg. per kilogram and 9 studies after doses of 0.4 mg. per kilogram. Propranolol was injected intravenously in doses of 0.2 mg. per kilogram over 1 minute, 10 minutes prior to acetylstrophanthidin testing. Twelve acetylstrophanthidin tolerance tests in as many animals were performed after pretreatment with propranolol. The parameters of acetylstrophanthidin intoxicating dose, recovery time from tachycardia to sinus rhythm, and the mortality rate were compared between control tests and pretreatment with beta blocking agents.

In order to obtain additional data with regard to survival from acetylstrophanthidin testing, an additional 10 animals were pretreated with the same dose of propranolol and an additional 18 animals were pretreated with a combination of propranolol

*Diphenylhydantoin sodium in the powdered form was diluted in 10 ml. of physiologic saline and the pH of the solution was adjusted to 11 by the addition of 1 drop of 5 per cent NaOH. The diphenylhydantoin was generously supplied by Parke, Davis and Company, Research Laboratories, Ann Arbor, Mich.

†MJ 1999 and propranolol in the powdered form was diluted in saline to 1 mg. per cubic centimeter. MJ 1999 was generously supplied by Mead Johnson Laboratories, Evansville, Ind. Propranolol was generously supplied by Ayerst Laboratories, New York.

0 2 mg per kilogram and atropine 2 0 mg Control acetylstrophanthidin tolerance tests were not performed in these animals.

Results

ACETYLSTROPHANTHIDIN INTOXICATING DOSE. Pigs given 5 and 10 mg per kilogram of diphenylhydantoin exhibited no obvious neurologic side effects. Animals receiving 20 mg per kilogram of diphenylhydantoin showed only transient nystagmus and ataxia lasting a few minutes. These symptoms usually had disappeared by the start of acetylstrophanthidin testing Animals who received 30 mg per kilogram of diphenylhydantoin exhibited persistent severe ataxia, nystagmus and often opisthotonus. Fig 2 depicts the mean diphenylhydantoin blood levels from animals of the 4 diphenylhydantoin pretreatment groups

Pretreatment with diphenylhydantoin in doses ranging from 5 to 30 mg per kilogram did not consistently alter the level of intoxicating doses in any of the groups studied (Fig 3) In only 5 of a total of 30 studies after diphenylhydantoin pretreatment were acetylstrophanthidin intoxicating doses increased by more than 0 5 mg (2 S D) over their own control values In 21 tests after diphenylhydantoin pretreatment acetylstrophanthidin intoxicating doses were within ±0 5 mg of control doses Four animals exhibited acetylstrophanthidin intoxicating doses which were lower than control values by 0 5 mg Furthermore, there was no significant change in mean intoxicating doses from control to pretreatment tests at the diphenylhydantoin doses studied (Fig 3)

Pretreatment of awake animals with MJ 1999 in doses of 0 2 and 0.4 mg per kilogram and propranolol in doses of 0 2 mg per kilogram also failed to protect the animal against acetylstrophanthidin-induced ventricular tachycardia. Prior administration of the blocking agents to animals produced neither a consistent nor significant increase in acetylstrophanthidin intoxicating doses (Figs. 4 and 5) In only 4 of 20 acetylstrophanthidin tolerance tests after MJ 1999 pretreatment and 4 of 11 tests after propranolol pretreatment were acetylstrophanthidin intoxicating doses increased by more than 0 5 mg (2 S.D) over control values. In 15 tests after MJ 1999 pretreatment and 7 tests after propranolol pretreatment acetylstrophanthidin intoxicating doses were within ±0.5 mg of control values. One animal pretreated with MJ 1999 and one animal pretreated with propranolol exhibited intoxicating doses which were lower by 0 5 mg than in control studies

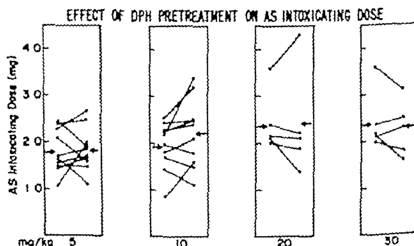


Fig 3 The effect of diphenylhydantoin (*DPH*) pretreatment on acetylstrophanthidin (*AS*) intoxicating dose The points on the left of each panel represent control values and those on the right values of acetylstrophanthidin intoxicating dose after diphenylhydantoin pretreatment. Each line connects control and pretreatment values for single animal. Arrows represent mean values for acetylstrophanthidin intoxicating dose for control and diphenylhydantoin pretreatment studies. Diphenylhydantoin doses in milligrams per kilogram are shown at the bottom of each panel.

RECOVERY TIME TO SINUS RHYTHM. The effect of diphenylhydantoin pretreatment on the recovery time from acetylstrophanthidin induced tachycardia to sinus rhythm is depicted in Fig. 6. Recovery time to sinus rhythm was shortened in 10 of 12 surviving animals who were pretreated with diphenylhydantoin at doses of 10 and 20 mg. per kilogram. Mean recovery times decreased from 12.4 to 6.1 minutes and from 8.0 to 4.7 minutes in the animals receiving 10 and 20 mg. per kilogram, respectively ($p < 0.05$). Recovery times for animals pretreated with smaller (5 mg. per kilogram) and larger (30 mg. per kilogram) doses were not significantly decreased (Fig. 6). Mean diphenylhydantoin blood levels from the 10 and 20 mg. per kilogram groups were 8.5 and 19.0 µg per milliliter, respectively.

Animals pretreated with MJ 1999 (0.2 and 0.4 mg. per kilogram) exhibited shortening of recovery times in 15 of 19 surviving animals (Fig. 7). Mean recovery times decreased from 10.0 to 6.0 minutes and 10.4 to 5.4 minutes in groups pretreated with 0.2 and 0.4 mg. per kilogram of MJ 1999 ($p < 0.05$). It was not possible to adequately assess recovery times in the animals pretreated with propranolol because of the high mortality rate (9 of 12 pigs).

MORTALITY. Figure 8 depicts the mortality rate from acetylstrophanthidin intoxication and pretreatment studies. In 50 control tests there was a mortality rate of 8 per cent. In a total of 30 diphenylhydantoin and 20 MJ 1999 pretreatment studies there was a mortality rate of 10 and 5 per cent, respectively. Death resulted from progression of ventricular tachycardia to ventricular fibrillation in the control, diphenylhydantoin, and MJ 1999 pretreated groups. A total of 22 acetylstrophanthidin intoxication studies were performed after pretreatment with propranolol and 15 deaths resulted for a mortality rate of 68 per cent. With propranolol pretreatment, death resulted from ventricular fibrillation in approximately ½ of these animals, and from ventricular standstill in the remaining animals. Ventricular standstill as a mechanism of death was peculiar to propranolol pretreated animals and was not noted in the other pretreatment groups. When atropine was given along with propranolol prior to the induction of acetylstrophanthidin in

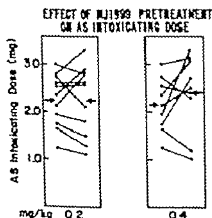


Fig. 4. The effect of MJ 1999 pretreatment on acetylstrophanthidin (AS) intoxicating dose. The points on the left of each panel represent control values and those on the right acetylstrophanthidin intoxicating doses after MJ 1999 pretreatment. Each line connects control and MJ 1999 pretreatment values for a single animal. Arrows represent mean values for acetylstrophanthidin intoxicating dose for control and MJ 1999 pretreatment studies.

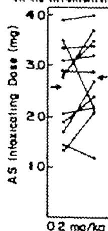


Fig. 5. The effect of propranolol pretreatment on acetylstrophanthidin (AS) intoxicating dose. The points on the left and those on the right of the panel represent values for acetylstrophanthidin intoxicating dose for control and propranolol pretreatment studies, respectively. Each line connects control and pretreatment studies in a single animal. Arrows represent mean values for acetylstrophanthidin intoxicating dose.

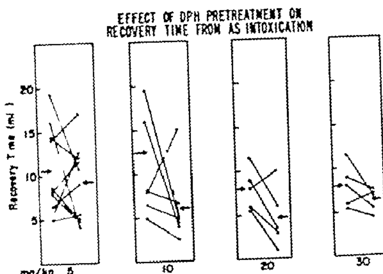


Fig 6 The effect of diphenylhydantoin (*DPH*) pretreatment on recovery time from acetylstrophanthidin-induced ventricular tachycardia to sinus rhythm The points on the left and those on the right of each panel represent values of recovery time from tachycardia to sinus rhythm for control and diphenylhydantoin pretreatment studies respectively Arrows represent mean values for recovery time for control and pretreatment studies Diphenylhydantoin doses in milligram per kilogram are shown at the bottom of each panel.

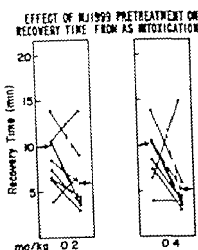


Fig 7 The effect of MJ 1999 pretreatment on recovery time from acetylstrophanthidin-induced ventricular tachycardia to sinus rhythm The points on the left and those on the right of each panel represent values for recovery time from tachycardia to sinus rhythm for control and MJ 1999 pretreatment studies respectively Arrows represent mean values for recovery time for control and pretreatment studies.

toxication the mortality rate decreased to control levels (Fig 8)

Discussion

Moses and Tyler[13] were the first to show the effectiveness of diphenylhydantoin in acutely abolishing ouabain induced arrhythmias in dogs with doses ranging from 10 to 30 mg per kilogram Recent clinical studies by Conn and Lang and colleagues have confirmed the clinical usefulness of diphenylhydantoin administered intravenously for digitalis arrhythmias. Beta sympathetic blocking drugs specifically pronethalol and propranolol have also been demonstrated to be of considerable value in the treatment of digitalis arrhythmias. Several investigators have noted, furthermore that larger doses of propranolol are required to reverse digitalis intoxication than epinephrine induced arrhythmias[n] and that a quinidine like mechanism may be operative in antagonizing arrhythmias precipitated by glycosides. Recently beta sympathetic blocking agents, such as MJ 1999 have been introduced which are supposedly devoid of quinidine like properties and specific for adrenergically induced arrhythmias.

The present study confirms the effectiveness of diphenylhydantoin and propranolol in the acute therapy of digitalis-induced arrhythmias. The dose of propranolol utilized in these experiments with awake unanesthetized animals is not unlike that utilized in clinical trials and is considerably less than that previously found to antagonize digitalis arrhythmias in anesthetized

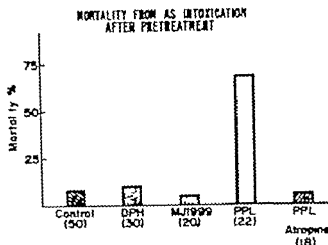


Fig. 8. The mortality rate from acetylstrophanthidin (AS) intoxication with drug pretreatment studies are shown. The bars indicate the mortality rate from control, diphenylhydantoin (DPH), MJ 1999, propranolol (PPL), and propranolol with atropine pretreatment. The numbers in parenthesis at the bottom of the figure indicate the number of tests performed with each drug regimen.

animal preparations. Of further note is that MJ 1999, previously considered to be specific for catecholamine arrhythmias but not digitalis arrhythmias, was as effective as propranolol in shortening the recovery time from acetylstrophanthidin-induced ventricular tachycardia in awake pigs.

Helfant and associates[4] found that diphenylhydantoin pretreatment in anesthetized dogs increased the dose of acetylstrophanthidin necessary to produce cardiac toxicity by 72 to 224 per cent. These authors concluded that diphenylhydantoin protected against the electrophysiological manifestations of digitalis excess without interfering with the inotropic action of glycosides and that diphenylhydantoin widened the toxic to therapeutic ratio of digitalis. Our data indicate that in the conscious pig, diphenylhydantoin pretreatment in doses ranging from 5 to 30 mg. per kilogram does not significantly increase the intoxicating dose of acetylstrophanthidin. The lack of a significant prophylactic action of diphenylhydantoin in acetylstrophanthidin toxicity in the awake pig is contrary to the dramatic protective effect previously described in anesthetized dogs. Of interest, however, is that animals pretreated with 10 and 20 mg. per kilogram of diphenylhydantoin with mean blood levels of 8.5 and 19.0 μg per milliliter exhibited shortened periods of intoxication although mean acetylstrophanthidin intoxicating doses were unchanged.

Mendez and associates demonstrated an increase in the lethal dose of acetylstrophanthidin in surgically sympathectomized adrenalectomized dogs. The influence of chemical sympathectomy by reserpine on digitalis tolerance has been studied and variable results noted. Several investigators have found that reserpinization increased the dose of digitalis necessary to produce ventricular arrhythmias in anesthetized dogs,[20] while others have described no prophylactic effect.[21] Reports of the protective effect of beta adrenergic blockade on digitalis toxicity in anesthetized animals have also been conflicting although the consensus in the literature has been that such compounds will increase the lethal dose of the glycoside. Aroesty and Cohen[7] found that the dose of the beta blocking agent, pronethalol, that immediately abolished digitalis-induced arrhythmias did not prevent ventricular tachycardia when given prophylactically 20 minutes before acetylstrophanthidin infusions in anesthetized dogs. Their results were contrary to the findings of Vaughan Williams and Sekiya,[22] who found that anesthetized guinea pigs pretreated with pronethalol tolerated larger amounts of oua

bain before developing ventricular tachycardia and death

Although both propranolol and MJ 1999 were effective in the acute therapy of acetylstrophanthidin induced tachycardia in the awake pig neither beta blocking agent when administered prophylactically consistently altered acetylstrophanthidin intoxicating doses. MJ 1999 pretreated animals demonstrated significant shortening of the time of acetylstrophanthidin intoxication. However propranolol when administered prior to acetylstrophanthidin testing was associated with a high mortality rate (68 per cent) from progression of ventricular tachycardia to both ventricular fibrillation and cardiac standstill. That atropine protected against this mortality suggests that overactive vagal influences might have been operative. The combination of acetylstrophanthidin induced vagal stimulation and beta adrenergic blockade with propranolol may have prevented the development of supraventricular escape rhythms or produced an additive negative inotropic effect on the ventricles.[22] The high mortality rate with propranolol pretreatment and the beneficial shortening of recovery time with MJ 1999 pretreatment were opposite and unexpected findings. Possibly propranolol in the doses used produced a more profound blockade of beta-adrenergic receptor sites and more pronounced myocardial depression than that associated with MJ 1999.

It is noteworthy that other animal studies evaluating the possible prophylactic effects of both diphenylhydantoin and propranolol [22] were carried out in anesthetized preparations. The addition of anesthetic agents, either because of intrinsic antiarrhythmic properties or by altering autonomic reflexes, might produce unrecognized changes on digitalis arrhythmias. For example Wallace and co-workers[3] noted that propranolol prolonged ventricular activation time in anesthetized preparations but not in awake animals. Their experiments indicated that beta blocking agents exerted quantitatively as well as qualitatively different effects in awake and anesthetized dogs. The problem of a synergistic effect of anesthesia with either diphenylhydantoin or the beta blocking agents studied was obviated in the present work by employing conscious unanesthetized animals.

Stock[22] described 15 patients with advanced myocardial disease who had one or more previous episodes of digitalis intoxication becoming intolerant to usual therapeutic doses of the drug. He found that pretreatment with propranolol 10 mg 3 times daily enabled 6 patients to receive full digitalizing doses whereas 5 patients did poorly with increasing congestive heart failure or hypotension. Our data in awake animals would seem to indicate that digitalization of patients receiving large doses of propranolol might well be hazardous particularly if overt digitalis intoxication is produced.

In conclusion several generalizations with regard to digitalis intoxication seem warranted from the present work. (1) The effectiveness of an antiarrhythmic agent in the treatment of digitalis-induced arrhythmias may bear no relationship to the protective ability of such an agent against toxic cardiac rhythms. (2) Our studies with MJ 1999 indicate that either this compound has antiarrhythmic properties apart from beta blockade i.e. quinidine-like effects or that pure beta adrenergic blockade may be beneficial in digitalis toxicity. (3) Pretreatment with propranolol decreased the lethal to toxic ratio of acetylstrophanthidin in awake animal. This observation would suggest that considerable caution should be exercised in the digitalization of patients receiving large doses of propranolol.

Summary

Treatment and pretreatment of acetylstrophanthidin-induced ventricular tachycardia was studied in awake pigs. The pharmacologic agents employed were diphenylhydantoin and 2 beta-adrenergic blocking agents, MJ 1999 and propranolol. These agents when administered intravenously at the onset of the arrhythmia significantly shortened the duration of acetylstrophanthidin induced ventricular tachycardia.

Pretreatment with diphenylhydantoin in doses ranging from 5 to 30 mg per kilogram failed to increase acetylstrophanthidin intoxicating doses. Pretreatment with MJ 1999 and propranolol likewise showed no

prophylactic effect on acetylstrophanthidin intoxication. Animals pretreated with MJ 1999 had a shorter duration of tachycardia, whereas animals pretreated with propranolol exhibited a high mortality rate. This increased mortality rate from propranolol pretreatment possibly resulted from more profound blockade of beta receptors or severe myocardial depression.

These findings indicate that diphenylhydantoin and beta-adrenergic blocking drugs, agents which are effective in the acute therapy of digitalis arrhythmias, do not protect against acetylstrophanthidin toxicity in awake pigs. MJ 1999, previously considered specific for catecholamine-induced arrhythmias, was found to antagonize acetylstrophanthidin toxicity by decreasing the duration of ventricular tachycardia. The high mortality rate with propranolol pretreatment may be relevant to clinical situations where digitalization is undertaken in patients receiving certain beta blocking agents.

REFERENCES

1. Conn, R. D.: Diphenylhydantoin sodium in cardiac arrhythmias, New England J. Med. 27?:277, 1965.
2. Lang, T. W., Bernstein, H., Barbieri, F., Gold, H., and Corday, E.: Digitalis toxicity. Treatment with diphenylhydantoin, Arch. Int. Med. 116:573, 1965.
3. Taylor, R. R., Johnston, C. I., and Jose, A. D.: Reversal of digitalis intoxication by beta-adrenergic blockade with pronethalol, New England J. Med. 271:877, 1964.
4. Helfant, R. H., Scherlag, B. J., and Damato, A. N.: Protection from digitalis toxicity with the prophylactic use of diphenylhydantoin sodium, Circulation 36:119, 1967.
5. Vaughan Williams, E. M., and Sekiya, A.: Prevention of arrhythmias due to cardiac glycosides by block of sympathetic beta receptors, Lancet 1:420, 1963.
6. Lucchesi, B. R.: Action of nethalide upon experimentally induced cardiac arrhythmias, J. Pharmacol. & Exper. Therap. 145:286, 1964.
7. Aronsty, J. M., and Cohen, J.: The effects of a beta-adrenergic blocking agent, pronethalol, on digitalis-induced ventricular arrhythmias, Am. Heart J. 71:503, 1966.
8. Sekiya, A., and Vaughan Williams, E. M.: A comparison of antifibrillatory actions and effects on intracellular cardiac potentials of pronethalol, disopyramide, and quinidine, Brit. J. Pharmacol. 21:473, 1963.
9. Epstein, S. E., and Braunwald, E.: Beta-adrenergic blocking drugs. Mechanisms of action and clinical applications, New England J. Med. 275:1106, 1966.
10. Somani, P., Fleming, J. G., Chan, G. R., and Lum, B.: Antagonism of epinephrine induced cardiac arrhythmias by 4-(2-isopropylamino-1-hydroxy-ethyl)-methanesulfonanilide (MJ 1999), J. Pharmacol. & Exper. Therap. 151:32, 1966.
11. Morris, J. J., Jr., Taft, C. B., Whalen, R. E., and McIntosh, H. D.: Digitalis and experimental myocardial infarction, Am. Heart J. In press.
12. Plaa, G. L., and Hine, C. H.: A method for the simultaneous determination of phenobarbital and diphenylhydantoin in blood, J. Lab. & Clin. Med. 47:649, 1956.
13. Mosey, L., and Tyler, M. D.: The effect of diphenylhydantoin sodium (Dilantin), procaine hydrochloride, procaine amide hydrochloride and quinidine hydrochloride upon ouabain-induced ventricular tachycardia in unanesthetized dogs, Circulation 10:65, 1954.
14. Turner, J. R. B.: Propranolol in the treatment of digitalis-induced and digitalis resistant tachycardias, Am. J. Cardiol. 18:450, 1966.
15. Lown, B., Gerr, W. M., and Orgain, E. S.: Use of a beta adrenergic receptor blocking agent (propranolol) in the treatment of cardiac arrhythmias, Am. J. Med. 43:161, 1967.
16. Somani, P., and Bachand, R. T.: Antiarrhythmic actions of propranolol in the dog heart-lung preparation, Am. Heart J. 4:222, 1967.
17. Lucchesi, B. R., Whitsitt, L. S., and Brown, N. L.: Propranolol (Inderal) in experimentally induced cardiac arrhythmias, Canad. J. Physiol. & Pharmacol. 44:543, 1966.
18. Mendez, C., Aceves, J., and Mendez, R.: Inhibition of adrenergic cardiac acceleration by cardiac glycosides, J. Pharmacol. & Exper. Therap. 131:191, 1961.
19. Roberts, J., Ito, R., Reilly, J., and Cavoll, V. J.: Influences of reserpine and βTM10 on digitalis induced ventricular arrhythmias, Circulation Res. 13:149, 1963.
20. Takagi, M., Zanuttini, D., Khalil, E., and Bellet, S.: Tolerance of reserpinized dogs to digitalis, Am. J. Cardiol. 15:203, 1965.
21. Yelnosky, J., and Ervin, R.: The effect of ouabain on cardiac automaticity in reserpine-pretreated dogs, Am. Heart J. 6?:687, 1961.
22. Sekiya, A., and Vaughan Williams, E. M.: The effects of pronethalol, dichloroisoprenaline and disopyramide on the toxicity to the heart of ouabain and anesthetics, Brit. J. Pharmacol. 21:462, 1963.
23. Dagget, W. M., Nugent, G. C., Carr, P. W., Powers, P. C., and Harada, Y.: Influences of vagal stimulation on ventricular contractility, O_2 consumption, and coronary flow, Am. J. Physiol. 212:8, 1967.
24. Wallace, A. G., Troyer, W. G., Lesage, A., and Zotti, F. F.: Electrophysiologic effects of isoproterenol and beta blocking agents in awake dogs, Circulation Res. 18:142, 1966.
25. Stock, J. P. P.: Beta adrenergic blocking drugs in the clinical management of cardiac arrhythmias, Am. J. Cardiol. 18:444, 1967.

The combined effect of atropine and β-adrenergic receptor antagonists on left ventricular function and coronary blood flow

Winifred G. Nayler, D.Sc.
I. McInnes, F.R.C.S., F.R.A.C.S.
Valerie Carson, M.Sc.
J. Swann, M.B., B.Sc.
T. E. Lowe, D.Sc., M.D., F.R.C.P., F.R.A.C.P.
Melbourne, Australia

The depressant effect of *dl*-propranolol on myocardial contractility, heart rate, and cardiac output is now well established.[1-4] However, the results of a recent clinical trial[5] indicate that some of the undesirable sequelae of propranolol administration, including the reduction in cardiac output, are eliminated if small doses of atropine are given together with the drug.

The mechanism whereby small doses of atropine eliminate or suppress the effect of propranolol on cardiac output is not clear. Stannard and co-workers[6] suggested that atropine may overcome some of the negative inotropic effect of propranolol, perhaps by preventing overactivity of the unmasked parasympathetic system, for ventricular function is depressed during vagal stimulation.[7]

In the following experiments, dogs on right-sided cardiac bypass have been used in an attempt to determine whether the depressant effect of *dl*-propranolol and another β-antagonist, Ciba 39 089-Ba (Trasicor), on ventricular function can be modified by atropine.

Methods

Left ventricular work function curves[11] were constructed for a series of dogs on right-sided cardiac bypass before and during the 30 minutes which followed the intravenous administration of either *dl*-propranolol or Ciba 39 089-Ba, with and without atropine. Healthy mongrel dogs (15 to 20 kilograms) premedicated with 30 mg. of morphine sulfate (intramuscularly) and anesthetized with sodium thiopentone (20 to 30 mg. per kilogram intravenously) were used. Ventilation was maintained with oxygen from a positive pressure respirator through a cuffed endotracheal tube at a rate of 2 L. per minute.

Experimental preparation. The exper-

From the Baker Medical Research Institute, Melbourne, Australia.
This investigation was carried out during the tenure of a grant-in-aid from the National Heart Foundation of Australia.
Received for publication May 27, 1968.

*Postal address: Baker Medical Research Institute, Commercial Rd., Prahran, 3181, Victoria, Australia.

mental preparation used, which is a modification of that originally described by Starling and associates,[12] has previously[9] been described in detail. Briefly, right-sided cardiac bypass was established as follows: cannulas were inserted into the superior vena cava through the proximal stump of the ligated vena azygos, into the inferior vena cava, and through the right atrial appendage; an inflow cannula was positioned in the main pulmonary artery. Venous return was collected, diverted to a reservoir, and then returned by means of a competent nonpulsatile pump to the pulmonary artery. Hence inflow to the heart could be controlled. Total coronary and Thebesian vein return was drained through a cannula inserted into the right ventricle, and coronary blood flow was measured by timed collection. After all dissection was completed and before cannulas were inserted, dogs were heparinized (2 mg. per kilogram per hour).

Left ventricular "work per minute" was calculated by the formula

$$W = Q\,(P_A - P_{LA})$$

where W = left ventricular "work" (in gram meters) per minute, Q = flow in milliliters per minute, P_A = mean systemic pressure measured in the femoral artery, and P_{LA} = left atrial pressure measured with a saline manometer. The term "work per minute" is used in accordance with its common cardiological use in the context of Frank-Starling work-study curves. Strictly speaking, the parameters are those of power, i.e., work per unit of time.

Arterial and coronary blood was sampled as required and the percentage of oxyhemoglobin estimated spectrophotometrically.[13]

Drugs. Dilutions of drugs were prepared in 0.9 per cent NaCl immediately before use; doses are expressed in terms of the salt. The following drugs were used: isoproterenol hydrochloride (as Isuprel, Winthrop Laboratories, Australia); *dl*-propranolol hydrochloride (as Inderal, Imperial Chemical Industries, Ltd., England); Ciba 39 089 Ba* (as Trasicor, Ciba Ltd., Basel, Switzerland); atropine sulfate (as Hermette, David Bull & Co., Australia);

*Ciba 39,089-Ba has the following formula: 1-(o-allyloxy-phenoxy)-3-isopropylamino-2-propanol hydrochloride.

and sodium thiopentone (as Pentothal, May and Baker Ltd., Australia).

Results

In preliminary control studies, inflow to the left atrium was increased in a stepwise manner by varying the pump output in increments of 10 mg. per kilogram per minute and calculated left ventricular work per minute was plotted against left atrial pressure. The resultant function curve had a steep slope, indicating that small increments in left atrial pressure resulted in large increments in left ventricular power. In six control experiments, successive function curves obtained during 90 minutes of control perfusion were not significantly ($p > 0.2$) different from those obtained initially. During this experimental period spontaneous changes in heart rate did not occur; after 90 minutes of perfusion, the mean heart rate, which was 146 ± 8 (S.E.M.) beats per minute, was not significantly different from that (143 ± 12 beats per minute) recorded initially.

Effect of dl-propranolol with and without atropine on left ventricular function and heart rate. Ten to 15 minutes after adding 0.1 mg. per kilogram of *dl*-propranolol to dogs on right-sided cardiac bypass, the heart rate had slowed significantly ($p < 0.005$) and left ventricular function curves were consistently displaced to the right and flattened. The mean results from 6 typical experiments summarized in Table I show that this dose of *dl*-propranolol depressed the power of the left ventricle over a wide work range. These results confirm those reported previously.

The mean results (± the standard error of the mean) of six other experiments in which left ventricular work function curves were established before and after adding this same dose of *dl*-propranolol together with 0.1 mg. per kilogram of atropine are summarized in Table I. Comparison of these results with those obtained when 0.1 mg. per kilogram of *dl*-propranolol was added without atropine indicates that the depressant action of *dl*-propranolol on ventricular power was not significantly modified by atropine ($p > 0.5$). Other data listed in Table I show, however, that atropine did modify the effect of *dl*-propranolol on heart rate. The mean heart rate

Table 1 Effect of 0.1 mg. per kilogram of dl-propranolol on left ventricular work per minute and heart rate

No. of experiment	Heart rate (beats/min.)	Left ventricular work (Gm. M./min.) — Left atrial pressure (cm. H_2O): 2	4	6	8	10	12	14
Control (6)								
Mean	144	122	186	280	340	440	480	510
±S.E.M.	±7.5	±16.0	±12.5	±11.0	±9.0	±11.5	±12.0	±14.[illegible]
After 0.1 mg. per kilogram of dl-propranolol (6)†								
Mean	112	90	145	175	210	240	245	F*
±S.E.M.	±9.0	±12.5	±11.0	±10.0	±14.0	±8.0	±9.0	
Sig.‡	++	+	+++	+++	+++	+++	+++	
Control (6)								
Mean	148	118	168	245	310	420	465	510
±S.E.M.	±8.2	±15.0	±14.0	±12.0	±11.0	±9.0	±7.0	±11.[illegible]
After 0.1 mg. per kilogram of atropine§ + 0.1 mg. per kilogram of dl-propranolol (6)								
Mean	142	86	140	162	198	220	238	F
±S.E.M.	±9.5	±11.6	±12.2	±9.0	±6.0	±9.5	±11.0	
Sig.	0	+	+++	+++	+++	+++	+++	

*F denotes failure indicated by a sudden marked rise in atrial pressure and a decline in the work per minute performed by the left ventricle and in the development of pulmonary edema.
†Left ventricular function curves were established before and 15 minutes after dl-propranolol had been added, with and without atropine.
‡Significance calculated with respect to control experiments for that series + $p < 0.01$; ++ $p < 0.005$; +++ $p < 0.001$; 0 $p >$ [illegible]
§Atropine added as atropine sulfate.

recorded after adding 0.1 mg. per kilogram of *dl* propranolol in the presence of atropine was 142 ± 9.5 beats per minute which was significantly ($p < 0.01$) higher than that recorded (112 ± 9.0) when this same dose of *dl*-propranolol was added without atropine. This dose of atropine alone, without any β-antagonist caused a small but significant ($p < 0.01$) increase in heart rate which increased from a control level of 147 ± 11 to 161 ± 9 beats per minute.

In other experiments, higher doses (0.3 mg. per kilogram) of *dl*-propranolol were used with and without atropine and the results from four separate experiments are displayed in Fig. 1, *A*. These results show that this dose of *dl* propranolol consistently caused the left ventricular function curves to be flattened and displaced to the right. Other results displayed in Fig. 1, *B* indicate that the addition of this same dose of *dl*-propranolol to another four preparations immediately after 0.1 mg. per kilogram of atropine had been added produced a similar response. The depressant action of 0.3 mg. per kilogram of *dl* propranolol on the left ventricular function over a wide range of left ventricular work was not significantly ($p > 0.5$) modified by 0.1 mg. per kilogram of atropine.

The heart rates in preparations to which 0.3 mg. per kilogram of *dl*-propranolol had been added without atropine, were significantly ($p < 0.001$) different from those in other preparations to which atropine and *dl* propranolol had been added. Thus, 15 to 20 minutes after 0.3 mg. per kilogram of *dl*-propranolol had been added

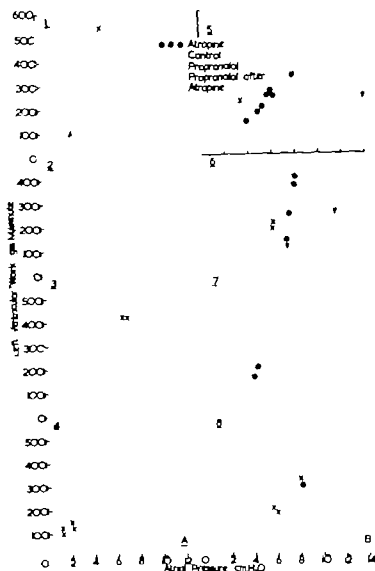


Fig. 1. Left ventricular function curves recorded from eight dogs on right sided cardiac bypass. A. Preps. 1 to 4 ventricular function curves recorded before and 15 minutes after adding 0.3 mg. per kilogram of dl-propranolol. B. Preps. 5 to 8 left ventricular function curves recorded before and immediately after adding 0.1 mg. per kilogram of atropine and again after adding 0.3 mg. per kilogram of dl-propranolol. The ability of the left ventricle to perform work was established at the indicated points.

to six bypass preparations, the heart rate had fallen from 145 ± 5 to 76 ± 6 beats per minute compared with a final heart rate of 118 ± 4 beats per minute which prevailed when this same dose of dl-propranolol was added either together with or immediately after 0.1 mg. per kilogram of atropine.

In these preparations, 0.1 mg. per kilogram of atropine consistently failed to have any direct effect on the ability of the left ventricle to perform mechanical work over the work range studied. Left ventricular function curves constructed for five preparations before and immediately after adding this dose of atropine are shown in Figs. 1, B and 3, B and indicate that atropine itself had no direct effect on left ventricular power.

Effect of Ciba 39,089 Ba with and without atropine, on left ventricular function and heart rate. Preliminary investigations indi

Table II. Effect of 0.1 mg. per kilogram of Ciba 39,089 Ba on left ventricular work per minute and heart rate

No. of experiment	Heart rate (beats/min.)	Left ventricular work (Gm. M./min.)						
		Left atrial pressure (cm. H_2O)						
		2	4	6	8	10	12	14
Control (6)								
Mean	147	125	176	274	336	452	498	56_
±S.E.M.	±12.0	±12.0	±14.0	±12.5	±14.5	±12.0	±16.0	12.8
After 0.1 mg. per kilogram of Ciba 39,089 Ba (6)								
Mean	90	120	168	268	305	418	476	538
±S.E.M.	±1 0	±11.0	±12.5	±11.0	±14.0	±12.0	±9.0	±11.8
Sig.†	++			+	+	+	+	+
Control (6)								
M	14	132	184	290	345	476	502	576
±S.E.M.	±8.0	±14.0	±12.0	±10.0	±10.0	±12.0	±14.0	±11.5
After 0.1 mg. per kilogram of atropine‡ + 0.1 mg. per kilogram of Ciba 39,089 Ba (6)								
Mean	126	126	175	274	312	438	480	563
±S.E.M.	±8.0	±14.0	±10.0	±8.0	±11.0	±9.0	±10.0	±11.8
Sig.	+			+	+	+	+	+

*Left ventricular function curves were established before and 15 minutes after Ciba 39,089-Ba had been added, with and without atropine.

†Significance calculated with respect to control experiments for the series: + $p < 0.01$; ++ < 0.001.

‡Atropine added as atropine sulfate.

cated that 0.3 mg. per kilogram of *dl*-propranolol and 0.1 mg. per kilogram of Ciba 39,089 Ba were equally effective in antagonizing the positive inotropic and chronotropic effects of 1.0 μg per kilogram of isoproterenol on dog heart muscle. Thus when isoproterenol was added to provide this concentration in the Tyrode solution bathing isolated electrically stimulated papillary muscles, the maximum tension developed during isometric contractions increased by 122 ± 8 per cent (12 experiments). When this same dose of isoproterenol was added after the prior addition of either 0.3 mg. per kilogram of *dl*-propranolol or 0.1 mg. per kilogram of Ciba 39,089 Ba, the maximum tension developed during contraction increased by only 2.5 ± 1.5 (6 experiments) and 2.2 ± 1.3 (6 experiments) respectively. In intact anesthetized dogs, the intravenous administration of 1.0 μg per kilogram of isoproterenol resulted in an increase in heart rate of 74 ± 6 (6 experiments) beats per minute. The similar addition of isoproterenol after the prior injection of either 0.3 mg. per kilogram of *dl*-propranolol or 0.1 mg. per kilogram of Ciba 39,089 Ba caused an increase of only 5 ± 1 (6 experiments) and 6.5 ± 1.5 (6 experiments) beats per minute, respectively. In the following experiments, therefore, the effect on left ventricular function of 0.1 mg. per kilogram of Ciba 39,089-Ba, with and without atropine, has been compared with that observed when the equipotent β-blocking dose (0.3 mg. per kilogram) of *dl*-propranolol was used.

Left ventricular function curves obtained 10 to 15 minutes after adding 0.1

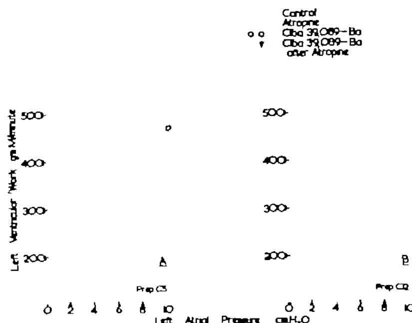


Fig. 2. Left ventricular function curves recorded from typical right-sided cardiac bypass preparations, (*A*) before and 15 minutes after adding 0.1 mg. per kilogram of Ciba 39,089-Ba, and (*B*) before and after adding 0.1 mg. per kilogram of atropine followed by 0.1 mg. per kilogram of Ciba 39,089-Ba. Left ventricular function was established at each indicated point.

mg. per kilogram of Ciba 39,089-Ba intravenously to dogs on right-sided cardiac bypass were slightly displaced to the right and on some occasions, slightly flattened. Ventricular function curves obtained from a typical preparation before and after adding this dose of Ciba 39,089-Ba are shown in Fig. 2,*A* and the mean results from similar experiments are summarized in Table II.

Comparison of these results with those already described for *dl*-propranolol shows that the depressant effect of Ciba 39,089-Ba on the power of the left ventricle over a wide range of work is significantly ($p < 0.01$) less marked than that caused by the equipotent β-blocking dose of *dl*-propranolol. This effect of Ciba 39,089-Ba on ventricular function was accompanied by a slowed heart rate; thus in six preparations, 15 minutes after this dose of Ciba 39,089-Ba had been added, the heart rate had fallen significantly ($p < 0.01$) from the control rate of 147 ± 12 to 90 ± 12 beats per minute. In other experiments, Ciba 39,089-Ba was added either together with or immediately after 0.1 mg. per kilogram of atropine and in these experiments, the effect of Ciba 39,089-Ba on ventricular function, as indicated by the ventricular function curves, was not significantly different ($p > 0.5$) from that observed when this β-antagonist was added without atropine. Left ventricular function curves recorded from a typical preparation before and after adding both atropine and Ciba 39,089-Ba are shown in Fig. 2,*B*. The effect of Ciba 39,089-Ba on heart rate resembled that described for *dl*-propranolol in that the heart rate recorded after adding Ciba 39,089-Ba either together with or immediately after 0.1 mg. per kilogram of atropine was 126 ± 8 beats per minute, which is significantly higher ($p < 0.01$) than that recorded (90 ± 12 beats per minute) when this same dose of Ciba 39,089-Ba was added without atropine. These results are summarized in Table II.

Effect of dl-propranolol and Ciba 39,089-Ba with and without atropine on coronary blood flow. Previous experiments have shown that *dl*-propranolol increases the resistance to blood flow in the coronary

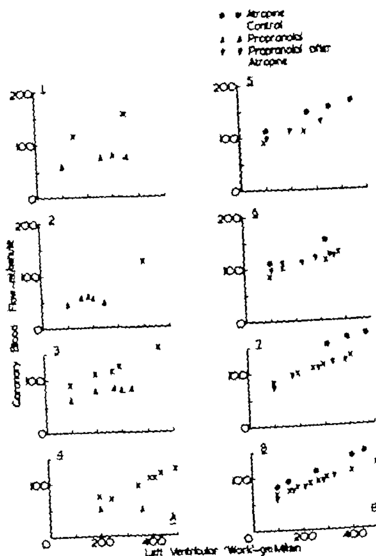


Fig 3 Effect of 0.3 mg per kilogram of *dl*-propranolol on coronary blood flow (*A*) in preps. *1* to *4* without atropine and (*B*) in preps. *5* to *8* after 0.1 mg per kilogram of atropine had been added Coronary blood flow was established at each indicated point.

circulation [?] and this effect of *dl* propranolol was confirmed during the present experiments. The results from four typical experiments shown in Fig 3 *A* indicate that 0.3 mg per kilogram of *dl*-propranolol caused a reduction in coronary blood flow throughout the whole of the work-study curve, and that *dl*-propranolol prevents the increase in coronary blood flow which under control conditions is induced by increasing left ventricular work per minute. When *dl*-propranolol was added either together with or immediately after 0 1 mg per kilogram of atropine, then coronary blood flow was fully maintained throughout the whole of the ventricular function curve The individual results of three such experiments, in which 0 1 mg per kilogram of atropine as atropine sulfate was added together with 0.3 mg per kilogram of *dl* propranolol are listed in Table III and show that coronary blood flow at the indicated levels of ventricular work was maintained under these conditions.

In other experiments, coronary blood flow was measured before and after adding atropine and again after adding *dl*-propranolol The individual results from four of these experiments are shown in Fig 3 *B* and the mean results from other ex

Table III *Effect of dl propranolol and Ciba 39 089-Ba with and without 0 1 mg per kilogram of atropine on the relationship between left ventricular work per minute and coronary blood flow*

N of experiments	Coronary blood flow (ml./min.) — Left ventricular work (Gm. M./min.) 100	200	300	400	500
dl Propranolol series					
Control (3)	95 ± 8	103 ± 6	136 ± 6 5	152 ± 8	168 ± 10
After 0.3 mg per kilogram of propranolol	59 ± 5	66 ± 5	82 ± 4	F	F
Control (3)	90 ± 4	169 ± 5	126 ± 5	131 ± 12	F
After 0 1 mg. per kilogram of atropine* + 0 3 mg per kilogram of dl-propranolol	91 ± 6	117 ± 8	122 ± 8	F	F
Control (3)	96 ± 1	109 ± 6	142 ± 8	166 ± 5	172 ± 9
After 0.1 mg per kilogram of atropine	112 ± 6	125 ± 5	156 ± 6	172 ± 8	186 ± 5
After 0 1 mg per kilogram of atropine† + 0 3 mg per kilogram of dl-propranolol	94 ± 5	106 ± 8	140 ± 5	F	F
Ciba 39,089 Ba series					
Control (4)	92 5 ± 5	104 ± 8	135 ± 5	154 ± 6	166 ± 4
After 0.1 mg per kilogram of Ciba 39,089-Ba	79 ± 3	85 ± 6	88 ± 6	94 ± 12	104 ± 9
Control (4)	98 ± 12	116 ± 6	126 ± 6	138 ± 5	145 ± 4
After 0 1 mg per kilogram of atropine + 0.1 mg per kilogram of Ciba 39 089-Ba	96 ± 5	118 ± 8	121 ± 9	135 ± 8	143 ± 5
Control (4)	88 ± 5	100 ± 4	126 ± 8	141 ± 7	156 ± 5
After 0.1 mg per kilogram of atropine	100 ± 5	112 ± 5	138 ± 9	162 ± 6	170 ± 8
After 0.1 mg per kilogram of atropine† + 0.1 mg per kilogram of Ciba 39,089-Ba	88 ± 8	102 ± 6	124 ± 6	140 ± 5	154 ± 8

*After atropine refers to 10 to 15 minutes after adding 0 1 mg per kilogram of atropine. After atropine + either dl-propranolol or Ciba 39,089-Ba refers to the simultaneous addition of these two drugs unless atropine had been added previously.
†Denotes that atropine had been added previously.

periments are listed in Table III In each of these experiments, atropine caused an increase in coronary blood flow throughout the whole of the ventricular function curve and in the presence of both atropine and *dl*-propranolol coronary blood flow increased with increasing levels of left ventricular work. Both *dl*-propranolol and Ciba 39,089-Ba counteracted the effect of atropine on coronary blood flow

When left ventricular work was plotted against coronary blood flow for preparations to which 0 1 mg per kilogram of Ciba 39 089-Ba had been added the resultant curve was consistently flattened relative to that obtained before adding the β-adrenergic receptor antagonist The results from a typical preparation are shown in Fig 4 *A* and the mean results show that 0 1 mg per kilogram of Ciba 39 089

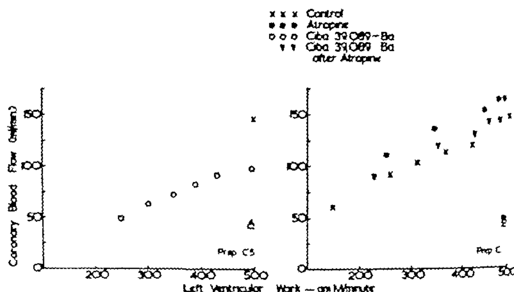


Fig 4 Effect of 0 1 mg per kilogram of Ciba 39,089 Ba on coronary blood flow (*A*) in typical preparation without atropine and (*B*) in another preparation after adding 0.1 mg per kilogram of atropine. Coronary blood flow was established at each indicated point.

Ba caused a significant ($p < 0.001$) reduction in coronary blood flow throughout the whole of the left ventricular function curve but did not prevent the increase in flow induced by increasing ventricular work. The coronary blood flow detected after adding this same dose of Ciba 39 089-Ba either together with or immediately after 0 1 mg per kilogram of atropine was not significantly different ($p > 0.1$) from that which occurred initially before either atropine or Ciba 39 089 Ba had been added The results from experiments in which coronary flow was established before and after the simultaneous addition of atropine and Ciba 39 089 Ba are summarized in Table III and in Fig 4 *B* left ventricular work per minute has been plotted against coronary blood flow for a typical preparation before and after the addition of 0 1 mg. per kilogram of atropine and 0.1 mg per kilogram of Ciba 39 089 Ba. During these experiments, 0 1 mg per kilogram of atropine alone consistently caused a small increase in coronary blood flow which was maintained throughout the whole of the work study curve, and a significant ($p < 0.01$) increase in heart rate.

Effect of dl propranolol and Ciba 39 089 Ba with and without atropine on myocardial oxygen consumption Data listed in Tables IV and V relating to coronary blood flow and coronary A V O_2 difference at the indicated levels of ventricular work per minute show the reduction in coronary blood flow caused by adding either β-propranolol or Ciba 39 089-Ba without atropine to be accompanied by a decline in the rate at which oxygen is extracted from the coronary circulation During these particular experiments, the output from the pump was monitored so that atrial pressure and hence ventricular filling pressure was kept constant. The decline in the gram-meters of work per minute performed by the ventricle after the β-antagonists were added therefore reflects the depressant effect of these drugs on ventricular function. Calculations of the ratio between the gram-meters per minute of work performed by these preparations and the oxygen extracted from the coronary circulation i.e. the oxygen "consumption index" (coronary blood flow X A V O_2 difference which reflects the oxygen utilized by the myocardium in performing this work) shows that both β-propranolol and Ciba 39 089-Ba increased this ratio Other data included in Tables IV and V indicate that although atropine effectively increases coronary blood flow

Table IV. Effect of dl-pr pranolol on coronary blood flow with and without at op ne*

Experiment	Heart rate (beats/m)	Coronary flow (ml./min.)	Coronary A-V O_2 difference (% saturation)	O_2 consumption index (coronary flow × A-V O_2 difference)	Work (Gm. M./min.)	Work/O_2 consumption index
Propranolol series						
Control	146	92	34	3 128	106 9	3 4
After 0.3 mg. per kilogram of dl-propranolol	78	66	21	1 386	76 7	5 5
				% change—55 6†		
Control	142	106	30 5	3 233	118	3 8
After 0.3 mg. per kilogram of dl-propranolol	82	64	22	1 408	80	5 7
				% change—47 1		
Control	135	98	27 5	2 695	116	4 3
After 0.3 mg. per kilogram of dl-propranolol	76	74	20	1 430	88 4	6 0
				% change—57 8		
Atropine + propranolol series						
Control	138	100 5	31 4	3 156	117	3 7
After 0.1 mg. per kilogr of tropine + 0.3 mg. per kilogram of dl-propranolol	116	99 0	21 4	2 118	95 2	4 5
				% change—32 8		
Control	146	96 5	26 4	2 547	96 8	3 8
After 0.1 mg. per kilogram of atropine + 0.3 mg. per kilogram of dl-propranolol	118	93 2	11 6	1 081	70 3	6 5
				% change—57 5		
Control	142	96 8	30 2	2 923	96 8	3 31
After 0.1 mg. per kilogram of tropine + 0.3 mg. per kilogram of dl-propranolol	120	95 0	16 8	1 596	86 2	5 4
				% change—45 3		

*Results presented as individual results from six separate preparations for which left ventricular function was established at fixed atrial pressure before and 10 minutes after adding either 0.3 mg. per kilogram of propranolol or the same dose of propranolol and 0.1 mg. per kilogram of atropine.

†The % change in O_2 consumption index was calculated

$$\frac{B-A}{B} \times \frac{100}{1}$$

where B refers to O_2 consumption before and A after adding propranolol with and without atropine as indicated.

*Table V Effect of Ciba 39 089 Ba on coronary blood flow with and without atropine**

Experiment	Heart rate (beat/min.)	Coronary flow (ml./m)	Coronary A-V O difference (saturation)	O consumption index (coronary flow × A-V O difference)	Work (Gm. M./min.)	Work/O consumption index
Ciba 39,089 Ba series						
Control	138	104 5	28 9	3 009	125	4 1
After 0 1 mg. per kilogram of Ciba 39 089 Ba	82	88 0	22 4	1 971	120	6 1
				% change 34 5†		
Control	146	98 6	33 2	3 274	116	3 7
After 0.1 mg per kilogram of Ciba 39 089-Ba	94	88 0	29 4	2 587	110	4 3
				% change—20 7		
Control	140	96 0	35 6	3 417	118 2	3 5
After 0 1 mg per kilogram of Ciba 39 089 Ba	102	79 0	31 4	2 499	113 6	4 5
				% change—26 8		
Atropine + Ciba 39,089 Ba series						
Control	136	92 0	32 4	2 980	132	4 4
After 0 1 mg per kilogram of atropine + 0.1 mg per kilogram of Ciba 39 089-Ba	129	90 6	25 0	2 263	126	5 6
				% change—23 9		
Control	138	104 6	30 2	3 158	120	3 8
After 0.1 mg per kilogram of atropine + 0.1 mg per kilogram of Ciba 39 089-Ba	127	102 2	24 4	2 491	116	5 1
				% change—20 8		
Control	145	112 6	27 5	3 096	120	3 9
After 0 1 mg per kilogram of atropine + 0 1 mg per kilogram of Ciba 39,089-Ba	134	109 8	22 0	2 415	115	4 8
				% change—22 7		

*Results presented as individual results from separate preparations [illegible] arterial pressure before and after adding [illegible] Ciba 39,089-Ba, with and without atropine [illegible].
†The % change in O consumption calculated as described in Table IV

under these conditions, the effect of *dl* propranolol and of Ciba 39 089-Ba on left ventricular power and on the ratio between ventricular work per minute and oxygen extracted from the coronary circulation remained unchanged

Discussion

These results indicate that, although atropine does increase coronary blood flow over a wide range of left ventricular function it does not modify the depressant effect of either *dl*-propranolol (Inderal) or Ciba 39 089-Ba (Trasicor) on left ventricular function, as indicated by left ventricular work-study curves. In addition the results show that the small dose of atropine used in these experiments does not itself have any direct action on left ventricular function and that quantitative differences exist between the myocardial depression caused by equipotent β-blocking doses of the two β-adrenergic antagonists used.

Although both *dl*-propranolol and Ciba 39 089-Ba depress the power of the left ventricle over a wide work range the ratio between the amount of cardiac work done (gram-meters per minute) and oxygen extracted from the coronary circulation was increased when either drug was added. The ratio between the amount of work per minute done and the oxygen consumed was increased after the β-antagonists were added, whether or not atropine was present so that although atropine itself increases both coronary flow and heart rate in these preparations, it does not modify the beneficial effect of β-antagonists on the relationship between cardiac work and oxygen utilization.

Other investigators[13] have reported that the intravenous injection of atropine results in a fall in venous pressure. The results of the present study would not be invalidated by such an effect, since venous return to the heart was controlled. The increase in coronary blood flow recorded after adding atropine may reflect a direct coronary vasodilator effect of this drug. Alternatively the increased coronary blood flow may result simply from the associated increase in heart rate. It is perhaps worth noting that while *dl*-propranolol and Ciba 39 089 Ba both decreased coronary blood flow the effect of *dl* propranolol on coronary flow differs from that of Ciba 39 089-Ba in that it seemed to prevent the increase in flow normally induced by increasing left ventricular work. The ability of atropine to prevent this effect of *dl*-propranolol may contribute to the reported benefit which arises from the combined use of atropine and *dl* propranolol.[8]

Left ventricular function, as indicated by left ventricular work-study curves was not significantly modified by atropine even though heart rate and coronary blood flow increased. Hence the use of small doses of atropine in studies which are aimed at determining the factors which influence and regulate cardiac function during selective autonomic blockade[1] probably can be justified. However both the β-antagonists used in this study depressed myocardial contractility and reduced coronary blood flow so that the results of experiments in which they have been used to gauge the influence of the autonomic system on myocardial function require careful appraisal.

The quantitative difference found between the relevant myocardial depressant effects of equipotent β-blocking doses of *dl*-propranolol and Ciba 39 089-Ba is in accordance with our earlier findings relating to the negative inotropic effects of these drugs on electrically stimulated isometrically contracting dog and human papillary muscle[1] and substantiates the conclusion that other factors in addition to β-adrenergic blockade are involved in the negative inotropic effect of these drugs. Since myocardial failure is recognized as one of the unwanted side effects[19-21] of *dl* propranolol therapy the availability of other β-adrenergic receptor antagonists which impair myocardial contractility to a lesser extent than does *dl*-propranolol and which have a beneficial effect on the ratio between myocardial work and oxygen consumption may be of practical significance.

Summary

The effect on the ability of the left ventricle to perform work of two β-adrenergic receptor blocking drugs, *dl* propranolol (Inderal) and Ciba 39 089-Ba (Trasicor) with and without atropine has been stud

ied over a wide range of work. Equipotent β-blocking doses of both drugs were used.

Both *dl* propranolol and Ciba 39 089 Ba depressed left ventricular function curves and displaced them to the right indicating a decrease in the ability of the left ventricle to perform work at a given filling pressure. The depressant effect of *dl* propranolol was significantly greater than that of an equipotent β-blocking dose of Ciba 39 089-Ba. Both β antagonists caused a decline in coronary blood flow, in heart rate, and in the rate at which O was extracted from the coronary circulation. Each increased the amount of work done by the myocardium per unit of oxygen extracted from the coronary circulation.

The depressant effect of either *dl* propranolol or Ciba 39 089 Ba on the ability of the left ventricle to perform work at a given filling pressure was not modified by atropine.

We gratefully acknowledge the skilled technical assistance of Mrs. I. G. Iversen, Miss C. Clarkson and Mrs. F. Mortensen. Supplies of Trasicor (Ciba 39 089 Ba) were generously donated to us by Ciba Ltd., Australia, and of Inderal (*dl*-propranolol) by Imperial Chemical Industries, England.

REFERENCES

1. Blinks, J. R.: Evaluation of the cardiac effects of several beta-adrenergic blocking drugs, Ann. New York Acad. Sc. 139:673, 1967.
2. Epstein, S. E., and Braunwald, F.: Clinical and haemodynamic appraisal of beta-adrenergic blocking drugs, Ann. New York Acad. Sc. 139:952, 1967.
3. Epstein, S. F., Robinson, B. F., Kahler, R. L., and Braunwald, E.: Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man, J. Clin. Invest. 44:1745, 1965.
4. Epstein, S. E., and Braunwald, F.: Beta adrenergic receptor blocking drugs, New England J. Med. 275:1106, 1966.
5. Stannard, M., Sloman, G., and Sangster, L.: The haemodynamic effects of atropine combined with propranolol in acute myocardial infarction, M. J. Australia 1:333, 1968.
6. Sloman, G., and Stannard, M.: Beta-adrenergic blockade and cardiac arrhythmias, Brit. M. J. 4:508, 1967.
7. De Geest, H., Levy, M. N., Zieske, H., and Lipman, R. I.: Depression of ventricular contractility by stimulation of the vagus nerve, Circulation Res. 17:222, 1965.
8. Levy, M. N., Ng, N., Lipman, R. I., and Zieske, H.: Vagus nerves and baroreceptor control of ventricular performance, Circulation Res. 18:101, 1966.
9. Nayler, W. G., McInnes, I., Swann, J. B., Race, D., Carson, V., and Lowe, T. E.: Some effects of diphenylhydantoin and propranolol on the cardiovascular system, Am. Heart J. 5:83, 1968.
10. Brunner, H., Hedwall, P. P., and Meier, M.: Influence of adrenergic beta-receptor blockade on the acute cardiovascular effects of hydralazine, Brit. J. Pharmacol. 30:123, 1967.
11. Sarnoff, S. F., and Berglund, E.: Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog, Circulation 9:706, 1954.
12. Stirling, G. R., Morris, K. N., and Race, D.: The effect of induced asystole on ventricular function, Australia & New Zealand J. Surg. 31:81, 1961.
13. Roos, A., and Rich, J. A.: Spectrophotometric determination of oxyhaemoglobin saturation and oxygen content of blood, J. Lab. & Clin. Med. 40:431, 1952.
14. Nayler, W. G., McInnes, I., Swann, J. B., Carson, V., and Lowe, T. E.: Effect of propranolol, a beta-adrenergic antagonist, on blood flow in the coronary and other vascular fields, Am. Heart J. 73:207, 1967.
15. Berry, J. N., Thompson, H. K., Edward Miller, D., and McIntosh, H. D.: Changes in cardiac output, stroke volume and central venous pressure induced by atropine in man, Am. Heart J. 58:204, 1959.
16. Ewer, H. E., Herrick, J. F., Mann, F. C., and Baldes, E. J.: The effect of atropine on the coronary blood flow of trained dogs, Am. J. Physiol. 139:683, 1943.
17. Jose, A. D., and Stitt, F.: Cardiac function after combined beta-adrenergic and cholinergic blockade, Circulation Res. 20 (suppl. III):33, 1967.
18. Jose, A. D.: Effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man, Am. J. Cardiol. 18:476, 1966.
19. Nayler, W. G., Chipperfield, D., and Lowe, T. E.: The inotropic effect of beta-adrenergic blocking drugs on human heart muscle, Cardiovas. Res. In press.
20. Stephen, S. A.: Unwanted effect of propranolol, Am. J. Cardiol. 18:303, 1966.
21. Shen, Y., Quiros, A. C., Burch, G. E., and De Pasquale, N. P.: Hemodynamic responses to beta-adrenergic blockade in dogs, Am. Heart J. 73:669, 1967.

Case reports

Pseudocoarctation of the aorta

Melvin H. Young, M.D.
Sun H. Lau, M.D.
Emanuel Stein, M.D.
Anthony N. Damato, M.D.
Staten Island, N. Y.

Pseudocoarctation of the aorta, an entity first reported in detail in 1951, is a seldom seen congenital structural defect of the aortic arch. Although it is becoming more frequently recognized, diagnosis may be missed because of unusual presenting features or failure to utilize appropriate diagnostic techniques. Consequently, improper management due to misdiagnosis is a hazard. The following is a case report of a patient with pseudocoarctation of the aorta whose presenting history was suggestive of a trauma related defect of the aortic arch.

Case report

V. B. (No. 151799), Puerto Rican man, was referred to our hospital because of an abnormality noted on routine posteroanterior chest roentgenogram. The patient's past history was remarkable in that he had been in an automobile accident 14 months prior to admission at which time he sustained injuries to his cervical spine and bruises to his anterior chest, all due to direct contact with the steering wheel. Following several days of hospitalization he was discharged improved with no resultant symptoms. Previous hospitalizations in 1946 and 1962 were necessitated by malaria and viral pneumonia, respectively. In 1941 the patient was accepted for military service following routine preinduction physical. At no time had he been advised of any structural defect in his chest.

Physical examination revealed a well-developed Puerto Rican man in no distress. Pulse rate was 84 and regular. Blood pressures revealed right arm pressure of 140 systolic, 86 diastolic, and left arm 142 systolic, 90 diastolic. The pressures in the lower extremities were identical, being 150 systolic, 90 diastolic. Examination of the skin revealed patchy vitiligo. The thoracic cage was of normal configuration. Examination of the lungs and heart revealed no abnormality except for a blowing ejection systolic murmur along the left sternal border in the fourth intercostal space. Abdominal and neurological examination was normal. The peripheral pulses were full and easily palpable. There was no pulse lag or diminished quality to the arterial pulsations in either the upper or lower extremities. Routine laboratory studies were normal. Admission posteroanterior and lateral views of the chest revealed a mass in the left superior mediastinum originally interpreted as either traumatic aneurysm or mass (Fig. 1). The possibility of a buckled aortic arch was also mentioned. Barium swallow revealed the mass to be distinct from the esophagus, thereby dispelling one observer's view that this might be either an enteric cyst or esophageal diverticulum. Cervical spine examination revealed old fracture of the transverse process of C 5 with spur formation. It was felt that an aortic arch study was indicated, and by Seldinger technique the aorta was entered via the left femoral artery. A No. 7 Kifa catheter was threaded into the descending thoracic aorta. However, the tip of the catheter continued to slip into the mass, which was obviously part of the aorta (Fig. 2). Because of the high pressure required for a good aortic arteriogram, it was elected to attempt a different approach for fear of tearing the aorta at its defect site. The procedure was then repeated via the right brachial artery; the tip of the catheter easily entered the ascending aorta proximal to the aneurysmal-like dilatation of the

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.

Received for publication Nov. 29, 1967.



Fig 1 The demonstrating posteroanterior and lateral roentgenogram revealing radiodensity adjacent to aortic arch Superior and posterior location in the mediastinum is demonstrated in the lateral view

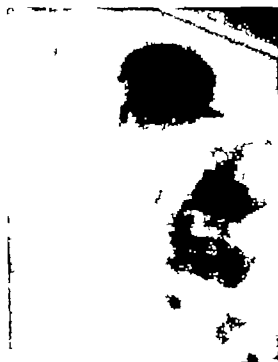


Fig Tip of the Kifa catheter entering the mass with ease demonstrating its direct communication with the descending thoracic aorta.

ortic arch A biplane aortogram using Schonander rapid changer was obtained and definitive diagnosis made (Fig 3)

Discussion

Pseudocoarctation of the aorta which appears in the world literature under such synonyms as buckling of the aorta,[7] congenital kinking of the aorta,[8] and atypical coarctation is a congenital defect of no hemodynamic significance, probably accentuated by senescence with tortuosity and dilatation The lesion is usually first diagnosed in a routine screening roentgenogram In the usual posteroanterior projection the anomaly appears as a superior mediastinal mass just to the left of the midline. The upper portion of this mass, which is smooth walled and pulsatile, is less radiopaque than the lower portion presumably due to the overlying lung tissue The upper portion of the mass represents the elevated and elongated aortic arch while the lower more opaque mass is probably that segment just distal to the kinking that moves anteriorly

The kinking occurs in the segment of the



Fig. 3. Biplane angiogram with dye in the thoracic aorta. The lateral view clearly illustrates the course taken by the thoracic aorta. Note that the integrity of the lumen is preserved.

aorta between the left subclavian artery and the ligamentum arteriosum (the aortic isthmus). Proximally the aorta ascends into the superior mediastinum to the left of the midline, while distally the aorta meanders posteriorly and to the left, then angulates acutely anteriorly and toward the midline. Poststenotic dilatation may or may not be seen. Calcium in the wall of the aorta in this entity has been reported but probably represents just a focal manifestation of a diffuse process. Calcification in the lesion alone has been reported but is unusual.

The defect itself is of no hemodynamic significance and the classical signs of aortic flow obstruction, i.e., diminished femoral pulses, pulse lag, hypertension of the upper extremities, and increased collateralization of the intercostal arteries, and internal mammary arteries do not occur. Clinically there is nothing in the history that suggests the diagnosis, and it has been found equally distributed in both sexes and in all ages. Physical examination is probably of some aid if an index of suspicion is present. In a recent report of eight cases,[7] a Grade 2/3 out of 6 ejection systolic murmurs at the base with radiation to the neck was heard in all cases. This murmur has been attributed to a change from laminar to turbulent flow in the region of the anomaly.[8] However, Steinberg[4] has stated that the murmur may be due to the presence of aortic valvular malformations. Various cardiac anomalies have been reported in association with pseudocoarctation of the aortic arch, such as a transposition of the great vessels, ventricular septal defect, aneurysm of the sinus of Valsalva, rheumatic heart disease, and bicuspid aortic valve.

The diagnosis is based on the characteristic findings on roentgenography, both routine and angiographic studies which shows the aorta assuming the characteristic shape resembling the figure three. The lumen is never encroached upon and there is no significant pressure gradient across the anomalous kinking. Edmunds and associates, have pointed out that subclinical coarctation is only indistinguishable from an indented isthmus. Since subclinical coarctation is related to aneurysm formation

this differential diagnosis assumes importance.

Management

Essentially, the management of this entity is its correct diagnosis. Since on a posteroanterior film the aorta may mimic tumors or true aneurysm, accurate identification of the true nature of this lesion is essential. This is attested to by the fact that there have been case reports in the literature where the entity was diagnosed as a mediastinal tumor and the patients were subject to radiation and surgery[2, 8] before the true nature of the lesion was established.

Steinberg[6] has suggested that prophylactic antibiotics be administered prior to dental work or surgery because of possible infection. Although there is no clinical data to confirm or deny this complication, the intact endothelial lining of the arch would seem to make blood-borne infections unlikely. Surgical intervention and the correction of the anomaly would seem to play no part in view of the normal hemodynamics and asymptomatic nature of this entity.

Summary

A report of an anomalous kinking of the aortic arch is presented with a discussion of the anatomy, physiology, diagnosis, and management. The congenital nature of the lesion, the importance of an accurate diagnosis, and hemodynamic insignificance are stressed in this report.

REFERENCES

1. Souders, C. R., Pearson, C. M., and Adams, H. D.: Aortic deformity simulating mediastinal tumor: subclinical form of coarctation, Dis. Chest. 20:35, 1951.
2. Stevens, G. M.: Buckling of aortic arch: roentgenographic entity, Radiology 70:67, 1958.
3. Griffin, J. F.: Congenital kinking of the aorta (pseudocoarctation), New England J. Med. 271:726, 1964.
4. Robb, G. P.: Atlas of angiocardiography, Am. Reg. Path., Washington, D. C., 1951, Armed Forces Institute of Pathology, p. 86.
5. Keller, H. I., and Cheitlin, M. D.: The occurrence of mild coarctation of the aorta (pseudocoarctation) and coarctation in one family, Am. Heart J. 70:115, 1965.
6. Steinberg, I.: Anomalies (pseudocoarctation) of the arch of the aorta. Report of 3 new and review of 8 previously published cases, Am. J. Roentgenol. 88:73, 1962.
7. Nasser, W. K., and Helmen, C.: Kinking of the aortic arch (pseudocoarctation). Clinical, radiographic, hemodynamic and angiographic findings in eight cases, Am. J. Med. 61:611, 1966.
8. Brewer, A. J.: Kinking of the aortic arch simulating mediastinal tumor, Brit. J. Radiol. 30:387, 1957.
9. Edmunds, L. H., Jr., McClenathan, J. E., and Hufnagel, C. A.: Subclinical coarctation of the aorta, Ann. Surg. 156:180, 1962.
10. Pattinson, J. N., and Grainger, R. G.: Congenital kinking of aortic arch, Brit. Heart J. 21:55, 1959.

Complete heart block of unknown etiology with complete recovery in a previously healthy 16-year-old boy

C. G. Kardinal, Lieutenant, MC, USN
Thomas B. Beach, Commander, MC, USN
Portsmouth, Va.

A great deal has been written in the recent medical literature with regard to the etiology and natural history of disorders of cardiac conduction. As recently as 5 to 10 years ago, it was generally agreed that arteriosclerotic heart disease with or without acute myocardial infarction was the leading cause of complete atrioventricular (A-V) block either permanent or transient.[1-4] Numerous other infectious as well as noninfectious causes were well recognized and a smaller group listed as idiopathic was always of necessity included. Recent clinical and autopsy studies[4-6] have cast considerable doubt upon the dominance of the role of arteriosclerotic heart disease (ASHD). In the cases studied, the most common lesion was not ASHD but a primary fibrosis of obscure origin predominantly affecting both bundle branches or the bundle of His. In these cases significant ASHD was absent and accounted for the etiology of the heart block in less than 20 per cent of the cases presented.

Complete heart block occurring in children is generally congenital in origin but has also been reported to have been acquired.[7]

The etiology of transient heart block has also received considerable attention, and its importance in acute myocardial infarction has been stressed.[8] Acute inflammatory disorders such as rheumatic fever, diphtheria, or viral myocarditis secondary to influenza, Coxsackie B infections, measles, mumps, rubella, infectious mononucleosis, etc., usually produce only a transient first or second degree block, but complete heart block is not unknown. Sarcoidosis[9-12] may produce transient or even permanent complete block, but the diagnosis of isolated cardiac sarcoidosis is rarely made ante mortem or in the absence of other characteristic clinical signs.

The case to be presented does not seem to fit well into any of the categories previously alluded to, and its specific etiology remains obscure.

Case report

P. M., a 16-year-old Caucasian boy, was completely well until 48 hours prior to admission when he developed a vague sensation of emptiness in his chest. This sensation was not associated with pain or shortness of breath. He continued to conduct his normal activities which consisted of attending classes in summer school. The morning of admission

From the Cardiopulmonary Function Laboratory, Department of Medicine, Naval Hospital, Portsmouth, Va.
The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or of the Naval Service at large.
Received for publication Dec. 4, 1967.

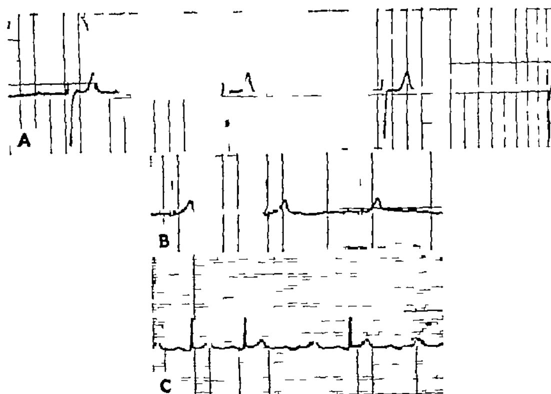


Fig 1 A Lead V taken i a dispensary showing high degree of A V block. P per speed 25 mm. per second B ECG monitor hythm strip on th fifth hospital day showing 2 1 A V block. C. Lead II following discharge f om the hospital showing a P R interval of 0 19 second.

while at school, he noted the onset of nausea and lightheadedness. H got p from class, walked into the hall, nd fainted. This episode of syncope was only momentary nd he quickly was aroused. H was taken home by his mother nd put to bed. A second episode of syncope occurred that sam morning while he was attempting to walk to the bathroom. H was taken to a dispensary d hortly after arrival he fell and had a generalized seizure. During this seizure he was noted to be pulseless, his chest was percussed with the return of a pulse t a rate of only 30 per minute. A electrocardiogram (ECG) was taken which demonstrated complete A V block with an trial rate of 120 per minute and ventricular rate of pproximately 30 per mi ut (Fig 1). An intravenous infusion of epinephrine in physiologic saline was begun, he was placed in an ambulance and taken to the hospital accompanied by a physician. Upon arrival t this hospital he was taken directly to the Cardiopulmonary Laboratory where transvenous bipolar pacing catheter was inserted. During the procedure, he again developed ventricular asystole and gain external cardiac resuscitation wa temporarily required.

He gave no history of prodromal pper respiratory tract infection, rheumatic fever or diphtheria. He participated actively in ports nd was member of his high school wrestling team

The past medical history was remarkable only in its absence of significant previous illness. A hernia repair was performed 8 months prior to the admission, and the anesthesia record documented the presence of normal pulse rate of 70 to 80 beats per min te.

There was no family history of heart disease, diabetes mellitus, or sudden death ECG obtained on each parent during his hospitalization were completely normal.

Physical examination after admission to the cardiac intensive care unit revealed a well-developed Caucasian boy in no distress with a transvenous pacing catheter in place through right antecubital cutdown The peripheral pulses are normal Blood pressure 115/75 in the right arm. Examination of the heart revealed no enlargement. The first and second sounds were normal, and there as a soft short Grade I apical systolic murmur hich radiated poorly Occasional atrial sounds were audible.

The following laboratory tests were negative or within the limits of normal white blood count, hemoglobin, hematocrit, total eosinophil count, urinalysis, L. E. cell preparations, blood urea nitrogen, creatinine, cholesterol total bilirubin, calcium, phosphorus, sodium chloride carbon dioxide, potassium protein-bound iodine, serum glutamic oxalacetic transaminase, VDRL, rheumatoid factor antinuclear antibody febrile agglutinins, total serum protein, and protein lectrophoresis A

sedimentation rate was 31 mm per hou (Wintrobe) Serial blood cultures revealed no growth throat culture grew out only normal flora Acute and convalescent serum for viral antibody titers against Coxsackie, ECHO adenovirus, and herpes simplex irses failed to show a significant rise in titer A chest roentgenogram revealed normal cardiac size and configuration and specifically did not demonstrate hilar adenopathy X-ray examinations of the hands were normal. Purified protein derivative intermediate histoplasmin 1.100 blastomycin 1.100 and coccidioidin 1 100 skin tests were all negative after discontinuation of steroid therapy An initial ECG as normal except for the complete A-V block.

He was placed at bed rest and monitored continuously in the cardiac intensive care unit. Treatment with prednisone 60 mg daily was initiated. Continuous transvenous pacing was required for the first 5 hospital days. On the fifth hospital day the initial complete A-V block gave w y to a lesser degree of A V block with 2 1 conduction (Fig 1), and continuous pacing was discontinued. Five to 6 hours after the development of 2 1 conduction, Wenckebach conduction developed, and persisted *with gradual transition to first degree block* (with a P R interval of 0 26 second) over an additional 6 to 8 hour period.

The pacemaker remained in place and he was continuously monitored for an additional 48 hours. The pacing catheter was removed, and he was gradually ambulated, and his steroid dose as slowly tapered to zero. Total duration of teroid therapy was 25 days. With continued close observation, his P R interval gradually diminished and by the ninth hospital day was 0.20 to 0.21 second. On about the eighth or ninth hospital day a normal sinus arrhythmia returned.

The balance of his hospitalization was unremarkable. He as active and asymptomatic on the ward. He was discharged and sent home after 30 day of hospitalization with a P R interval of 0 19 to 0.20 second. He was seen in follow-up 2 months after being discharged *from the hospital and* ECG as taken (Fig 1). The P R interval remains 0 19 to 0.22 second and the ECG is otherwise within normal limits as upon admission. H feels all, has returned to school, and specifically asked if he could return to restling It was recommended only that he not participate in competitive thletics

Discussion

This case closely parallels 2 cases reported by Sissman[13] in that they each presented with Adams-Stokes attacks and each had transient documented asystole. An important difference is present however in that each of his 2 cases had a prodromal respiratory tract infection, and each was left with a residual right bundle branch block. This case also seems to parallel to a degree 2 cases of sudden death in young athletes reported by James and associates.[14,15] Careful autopsy studies in these cases demonstrated degenerative lesions in the sinus node and hyperplasia and obstruction lesions in its nutrient vessels with only minor changes elsewhere in the heart. It is interesting at this point to speculate that our case may have been secondary to a focal vascular or inflammatory lesion in the area of the A V node from which he was fortunate enough to completely recover

The role steroids played in his recovery is again unknown but the fact that steroids can and do influence A V conduction has been well established [4] Steroids of course may act by decreasing inflammatory reaction and edema about the A V node, but they also act by increasing the conductive systems sensitivity to epinephrine and norepinephrine [17] as well as having a direct effect on the node itself [18]

We think the prognosis is favorable. Our optimism has been re-enforced by the reporting by White and Donavan[1] of a case of acute transient heart block secondary to an infectious process in a 24-year-old law student who 41 years after his illness was completely well and in sinus rhythm

The importance of the role of localized vascular or inflammatory lesions of the cardiac conduction system in the production of Adams-Stokes attacks seizures and asystole with sudden death in young adults is unknown but one should be aware that such conditions do occur and are potentially salvable with proper treatment.

Summary

A case of acute complete heart block in an otherwise healthy 16-year-old Caucasian boy was presented There was complete recovery wh ch was probably influenced by adrenal steroid therapy A brief discussion of the possible pathogenesis is included

The authors ish to express their ppreciation to Captain J J Dempsey MC USN Lieutenant J G Gracey MC, USNR Robert H Peter M D and Mrs. Rebecca Combs for their assistance in preparation and review of this manuscript.

REFERENCES

1 Penton, G. B Miller H., and Levine, S. A Some clinical features of complete heart block, Circulation 13:801, 1956
2. Bellet, S Clinical disorders of the heart beat, Philadelphia, 1963, Lea & Febiger Publishers, pp. 340-366
3. Lev M Anatomic basis for trioventricular block, Am. J Med. 37 742, 1964.

4. Zoob, M and Smith, K. S. The aetiology of complete heart-block, Brit. M J 2 1149 1963
5 Lenegre, J and Moreau, P Complete auriculoventricular block. It causes and lesions, Bull. Soc. Med. Hop. Paris 113 797 1962.
6. Nakamura, F F., and Nadas, A. S. Complete heart block in infants and children, New England J Med. 270 1261 1964
7 Paul, M H Cardiac arrhythmias in infant and children, Progr Cardiova Dis. 9 136, 1966
8. Jackson, A. E and Bashour F A Cardiac arrhythmias in acute myocardial infarction complete heart block and its natural history Dis. Chest 51:31 1967
9 Moyer J H and Ackerman A. J Sarcoidosis, a clinical and roentgenological study of 28 cases, Am. Rev Tuberc. 61:299 1950.
10. Peacock, R A Lippschutz, E. J and Lukas, A. Myocardial sarcoidosis, Circulation 16:67 1956.
11 Phinney A O J Sarcoid of the myocardial septum with complete heart block. Report of two cases, Am Heart J 62:270, 1961
12. Clinical Pathologic Conference of the Naval Hospital, Portsmouth, Va., U.S. Armed Forces Med. J 8:855, 1957
13 Sissman, N J Stokes-Adams syndrome in childhood two cases of nonsurgically acquired origin, Am. J Dis. Child. 110:658, 1965.
14 James, T N Froggatt, P and Marshall, T K.: Sudden death in young athletes, Ann Int. Med. 67:1013 1967
15 James, Thomas N Personal communication.
16 Dall, J L.: The effect of steroid therapy on normal and abnormal atrio-ventricular conduction Brit. Heart J 26:537 1964.
17 Landegren J., and Biorck, G.: The clinical assessment and treatment of complete heart block and Adams-Stokes attacks, Medicine 42 171 1963.
18. Lown, B Arons, W L., Ganong, W F Vazifdar J P and Levine, S. A.. Adrenal steroids and auriculoventricular conduction, Am Heart J 50 760, 1955
19 White, P D and Donavan, H.: Hearts their long follow-up, Philadelphia, 1967 W B Saunders Company pp. 1 2.

Clinical pathologic conference

Peter Harris M.D F.R.C.P
Donald Heath M.D M.R.C.P M C Path
Paul Davison M.D F.R.C.P
Birmingham England

Clinical abstract

DR. DAVISON A young woman 21 years of age as admitted to hospital in Birmingham on April 19 1967 She had been blue and breathless from birth. Up to the age of 7 years, she had been dyspneic after walking only few teps and, in 1953 she was admitted to the hospital for surgical treatment. Following this, her color improved and she was able to walk ¾ mile, play games, and climb stairs without too much discomfort. She trained as shorthand typist. In 1963 however her excellent progress came to halt when she required urgent treatment in hospital in Shrewsbury her home town. Following this, her breathlessness increased. In 1964 her ankles began to swell nd this condition persisted. She began to cough up blood in November 1966.

On examination, on her admission to hospital in Birmingham, she had pronounced central cyanosis, ith gross clubbing of the fingers and toes. There as report of "marked neck and suprasternal pulsation. Her systemic blood pressure as 120/70 mm. Hg Her radial pulse rate was 80 per minute the pulse was regular and of good olume. When sitting upright in bed, the jugular venous pressure was raised 4 cm above the sternal notch. The apex beat as felt in the mid-clavicular line in the fifth left intercostal space. There was parasternal impulse. The first sound was split in the apical region and the second sound was split at the base. There was a systolic murmur t the apex, but no thrills were present. An inconstant faint machinery murmur was udible in the second left interspace 1 inch from the sternal edge. The chest as resonant to percussion. There were no basal crepitations. There were no abnormal physical signs referable to the bdomen or t the central nervous system

On April 26, cardiac catheterization was carried out. Following this investigation, she became very pale nd breathless. After 5 min tes, she became unrousable and her pulse nd systemic blood pressure ere not recordable. She responded to treatment, nd later that night her pulse rate was 120 per minute. Systolic blood pressure was 70 mm. Hg

On the following day she was given further treatment. Her systolic blood pressure had risen to 120 mm. Hg She was drowsy but there were no signs referable to the central nervous ystem

On M y 1 she developed cramp-like pains in the left calf She had pain in the chest and an irritating cough. The following day the left lower leg became warm and swollen, and treatment for this was started. At 6 30 P.M. and at midnight, a few hours after starting treatment, she had large hemoptyses.

The following day May 3 the left leg remained painful, and treatment was restarted Further hemoptyses occurred

On May 11 t 10 15 P.M., she coughed up more blood became very dyspneic, and lost consciousness. Her pulse rate was 80 per minute. The systemic systolic blood pressure was recorded as 80 mm Hg She developed gallop rhythm. By 10 45 P.M., she was deeply nconscious A lumbar puncture was performed. She died t 4 15 A.M. on May 12

Investigations On April 20 1967 hemoglobin was 21.6 Gm. per cent packed cell olume was 77 per cent and mean corpuscular hemoglobin concentration was 28 per cent. Erythrocyte sedimentation rate (Westergren) was 1 mm. per hour and the wh te cells were normal in morphology and distribution.

Discussion

PROF HARRIS Perhaps I should say immediately that I am not by training a "congenital cardiologist because I am certain from reading the clinical summary that we are dealing with a case of congenital heart disease. This girl was blue and breathless from birth. If we exclude shunts in the lung she must have had a shunt of blood from the right to the left side of the heart through a defect such as a patent ductus

From the Medical School, University of Birmingham, Birmingham, England
*Simon Marks Professor of Cardiology Institute of Cardiology University of London.

arteriosus a ventricular septal defect or an atrial septal defect. Under normal circumstances, the pressures in such defects are such that the blood flows from left to right so that we must postulate the existence of an added factor to explain the flow of blood in the opposite direction

One determining factor is the relative resistances of the systemic and pulmonary circulations. Thus, if the pulmonary vascular resistance becomes raised the flow will be reversed from pulmonary artery to aorta. This is associated with structural changes in the small pulmonary arteries which progress from medial hypertrophy through obstructive intimal lesions, to bizarre dilatation lesions. Such hypertensive pulmonary vascular disease takes time to develop however and even a large patent ductus arteriosus or ventricular septal defect does not cause reversed flow of blood from birth Hence I believe that we can exclude the possibility of a congenital cardiac shunt with pulmonary hypertension and a reversed shunt in this case. We may nevertheless, need to return to these hypertensive vascular lesions later on to explain the clinical features of this case

A second factor to explain the reversal of blood flow may be a mechanical obstruction say in the form of pulmonary stenosis, which will lead to preferential flow into the aorta The combination of pulmonary stenosis at the valvular or subvalvular level with a septal defect is not uncommon. The commonest lesion here is Fallot s tetrad Another possibility is tricuspid atresia where blood flows from right to left through an atrial septal defect to the left atrium and left ventricle usually there is associated pulmonary stenosis. A combination of atrial septal defect and pulmonary stenosis is quite common, but again, cyanosis usually occurs later in life. Mixing of streams of blood with the flow of deoxygenated blood into the aorta also occurs in persistent truncus arteriosus or transposition of the great vessels. It seems likely even in persistent truncus, that there must be some diminution of blood flow to the lungs to produce cyanosis, say with a sole bronchial arterial supply to the lung Even in transposition the great flow prevents all but minimal cyanosis unless there is associated pulmonary stenosis. There are many rare forms of cyanotic congenital heart disease, but we have considered the most likely ones.

In 1953 she had surgical treatment. In general such treatment for congenital heart disease may be either palliative or corrective. At that time the surgical treatment most likely to have been carried out was palliative to increase the flow of blood to the lungs. This would have been done by the creation of a systemic pulmonary anastomosis such as by the Blalock Taussig or Pott s operations. The impact that this type of surgery had on cyanotic congenital heart disease is well demonstrated in this case, for her life was changed into an active one for 10 years, and she was able to train as a shorthand typist.

Then in 1963 her excellent progress came to a halt and she needed urgent treatment. If she had Fallot s tetrad she might have developed a paradoxical embolus or even more likely a brain abscess.

Her breathlessness increased and her ankles began to swell, presumably because she developed congestive cardiac failure. She also coughed up blood Why should she do this with diminished pulmonary blood flow? Had she developed significant pulmonary hypertension as a result of the creation of too large a systemic-pulmonary anastomosis with a pathological increase of pulmonary flow? If pulmonary vascular resistance increased the initial left-to-right flow through the anastomosis might be diminished and then even reversed

As to the physical signs, her increased neck pulsation with a systemic blood pressure of 120/70 mm. Hg leads me to believe it was venous rather than arterial in nature This might be due to a raised pressure in the right atrium and neck veins with accentuated normal "a" and "v" waves. There might be obstruction of blood flow out of the right atrium making the a waves abnormally high Finally she may have developed dilatation of the tricuspid ring due to right ventricular hypertrophy and dilatation leading to tricuspid incompetence. The jugular venous pressure was raised so she was in congestive cardiac failure.

The left parasternal impulse implies right ventricular hypertrophy I note, that the first cardiac sound was split. Normally the

sound does have 2 components. An alternative explanation is that after the first sound there was an extra clicking noise due to an impact of blood coming from a hypertrophied ventricle into a dilated aorta as in Fallot's tetrad or a persistent truncus.

It is difficult to explain why the second sound at the base was split. All the abnormalities I have considered have one thing in common that the second sound at the base is single. A phonocardiogram in Fallot's tetrad may show splitting of the second sound with an asynchronous closure of the aortic and pulmonary valves because the right ventricle empties more slowly than normal and the closure of the pulmonary valve is delayed. Normally this is not sufficiently loud enough to be heard. If she had developed pulmonary hypertension, this might give rise to an audible pulmonary component of the second sound. There was a systolic murmur at the apex and I think it likely that this was due to a tricuspid leak. If pulmonary stenosis was present, one would have expected the murmur in the pulmonary area.

An inconstant faint machinery murmur was audible in the second left interspace. This implies a systemic pulmonary shunt which could be due to either the artificial shunt or an abnormal bronchial circulation. One would have expected the murmur to be loud and consistent if it had been due to the surgical shunt but it may have been modified by the development of pulmonary hypertension.

Finally she had a cardiac catheterization on April 26. Following it, she became pale and breathless and her pulse and blood pressure were unrecordable. I think it most likely that this girl was critically ill with congestive cardiac failure and had a simple vasovagal attack. This led to a critical lessening of pulmonary blood flow and hence, to serious cerebral hypoxia. Paradoxical thromboembolism is a less likely alternative. She responded readily to treatment and there were no signs in the central nervous system to indicate the presence of an embolus.

Then on May 1 she developed cramp-like pains in the calf pain in the chest and an irregular cough. It is evident that she had a venous thrombosis and I am sure that her doctors felt that they had to treat this with anticoagulants. A few hours later she had a large hemoptysis and presented the clinicians with a terrible dilemma. If the hemoptysis was due to embolism the correct treatment was anticoagulation. If the hemoptysis was due to local pulmonary arterial disease, the correct treatment would be not to give anticoagulants. Also, these patients with polycythemia may have an abnormally low platelet count so that



Fig. 1. Radiograph of chest taken on April 20, 196 showing coeur en sabot, dextroaorta, pulmonary oligemia, and evidence of previous left-sided thoracotomy.



Fig. 2. Angiocardiogram taken on April 26, 1967. There is over-riding aorta with dextroaorta. A large tortuous left internal mammary artery is anastomosed to the left pulmonary artery. There is no sign of pulmonary trunk, the pulmonary arteries are small, and the lungs are oligemic.

they have prolonged clotting and bleeding time making the use of anticoagulation difficult More hemoptyses occurred and she became unconscious and died In conclusion from the clinical history I believe she had Fallot s tetrad with an artificial systemic pulmonary anastomosis which had led to pulmonary hypertension

May I now see some radiographs of the chest? Well the radiograph taken on April 20 (Fig 1) shows right ventricular hypertrophy and there is no shadow of a pulmonary trunk These are the appearances of so called coeur en sabot The lung fields are oligemic There is also radiographic evidence of the previous left thoracotomy These features are consistent with Fallot s tetrad with a right sided aortic arch The pulmonary oligemia suggests that my conjecture that she had pulmonary hypertension due to an abnormally high flow through the anastomosis was wrong Perhaps this had become blocked by thrombus.

DR DAVISON Here is the electrocardiogram (ECG) taken on the same day

PROF HARRIS This shows sinus rhythm and right axis deviation and confirms the presence of right atrial and right ventricular hypertrophy

DR DAVISON Here are some angiocardiograms in sequence taken during cardiac catheterization (Fig. 2)

PROF HARRIS These are of interest So far as the aorta and its branches are concerned the angiocardiogram shows an over riding aorta, dextroaorta and a dilated tortuous artery arising from the aorta and clearly passing to the left lung presumably to be anastomosed to the left pulmonary artery

DR. DAVISON The surgeon described the vessel as an aberrant left internal mammary artery

PROF HARRIS The angiocardiogram shows no sign of a pulmonary trunk. The pulmonary arteries appear to be very small and the lungs are oligemic. I am wondering if she had developed some lesion like wide spread thrombosis in the small pulmonary arteries preventing blood getting to the lungs.

PROF D ABREU Was a blood culture done at any time?

DR DAVISON No. She was never febrile.

PROF BREWER What blood pressures were recorded at the cardiac catheterization?

DR. DAVISON The pressure in the right atrium (mean) was 5 mm Hg and in the aorta was 125/75 mm. Hg We found that the catheter passed easily from the right ventricle into the aorta but despite repeated attempts we could not enter the pulmonary trunk from the right ventricle. The oxygen saturation in the right atrium was 43 per cent and in the aorta 59 per cent.

MR. MAYOU What did the cerebrospinal fluid show?

DR. DAVISON It was a clear colorless fluid with one white cell per cubic millimeter There was 156 mg of glucose per 100 ml 20 mg of protein per 100 ml. and 736 mg of chloride per 100 ml. Do you think that the worsening of cyanosis was associated with puberty and increased oxygen demand?

PROF HARRIS It might well have been since the valve orifice grows as a function of the square of the radius, whereas body oxygen requirements grow as a function of the cube of the bodily dimensions.

DR. ALLISON Is it not possible that the recurrent hemoptyses were due to multiple pulmonary thromboses rather than pulmonary hypertension? Diminished pulmonary flow and associated polycythemia could certainly account for such widespread pulmonary thrombosis.

PROF HARRIS Certainly pulmonary thrombosis is common in Fallot s tetrad and increases with age. I don t know however if they give rise to hemoptyses. However it is certainly true that the thrombotic lesions do not give rise to pulmonary hypertension. We must remember that hemoptysis can occur in Fallot s tetrad without pulmonary hypertension.

DR. DAVISON Perhaps we can now ask Dr Heath to tell us what he found at the post mortem

DR. HEATH The body was that of a slightly built girl showing cyanosis of the mucous membranes and clubbing of the finger and toenails. The heart was considerably enlarged The right atrium was dilated. The tricuspid valve was normal in structure but the valve orifice was dilated. The right ventricle was dilated and hypertrophied its thickness being 13 mm. There was a large membranous ventricular septal de-



Fig. 3 The heart has been opened through the hypertrophied right entricle and over-riding ascending aorta to show the large membranous ventricular septal defect

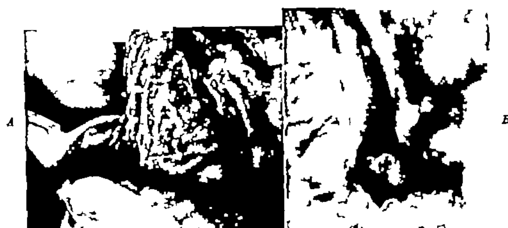


Fig. 4 *A* Dissected great vessels. T the left is the thick walled aorta. T the right is the thin-walled pulmonary trunk showing the features of coarctation of the pulmonary artery *At the origin of this is the atretic* pulmonary valve. *B* The tretic pulmonary valve with hypoplastic pulmonary trunk arising bove it.



Fig. 5 The systemic-pulmonary nastomosis. The aberrant left internal mammary artery is show to the left. The thin-walled pulmonary artery is show to the right. Th pms hav been inserted slightly to the left of the site of anastomosis.

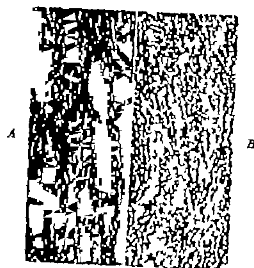


Fig 6 Transverse sections of the 2 great vessels stained to show their elastic tissue pattern (Both Elastic/Van Gieson ×100) A Aorta There is a dense network of parallel long elastic fibrils. B Pulmonary trunk. There is a sparse network of short clumped elastic fibrils



Fig 7 Transverse section of left internal mammary artery used in the systemic-pulmonary anastomosis. The internal elastic lamina is disrupted due to organization of superimposed thrombus The media is of typical systemic structure. (Elastic/Van Gieson ×50)

fect allowing free communication between the 2 ventricles (Fig 3) The pulmonary valve was minute and atretic (Fig 4) Arising above this was a small thin walled pulmonary trunk showing the features of the so-called coarctation of the pulmonary trunk (Fig 4) This passed upward and to the left of the aorta and then divided into two The hypoplastic right pulmonary artery passed behind the ascending aorta to the right lung The hypoplastic left pulmonary artery passed to the left lung It had been anastomosed to an aberrant left internal mammary artery (Fig 5) Distal to the site of the systemic-pulmonary anastomosis the left pulmonary artery was dilated but still thin walled The venae cavae and the pulmonary veins were normal The left atrium was of normal size The mitral valve was normal in structure and circumference. The left ventricle was normal in thickness. The aorta was overriding The aortic valve was normal in structure but was dilated Both ventricles communicated with the aorta, and with one another through the ventricular septal defect

The lungs were congested and there were large hemorrhages into the parenchyma consistent with having followed anticoagulant therapy The brain was deeply congested So too were all the abdominal viscera including the spleen and kidneys The liver showed the nutmeg pattern of chronic passive venous congestion and the fatty element of this was more pronounced than usual.

It is of some interest to consider the structure of some of the arteries concerned in this case.

The thick walled *aorta* showed a normal dense network of elastic tissue in its media composed of roughly parallel long elastic fibers (Fig 6, *left*) The hypoplastic *pulmonary trunk* showed a characteristic "hypotensive configuration generally associated with states of diminished pulmonary arterial pressure and flow (Fig 6 *right*)[1] The elastic tissue was sparse and clumped together The *left internal mammary artery* showed the characteristic structure of a muscular systemic artery with a well defined muscular media with 2 distinct elastic laminae There was heaped up intimal fibrosis in this vessel which was found to be due to organization of thrombus with disruption of the underlying internal elastic lamina (Fig 7) The *small pulmonary arteries* were very thin walled and contained eccentric nodules of organized thrombus (Fig 8) This histological picture is highly characteristic of diminished pulmonary arterial pressure and flow with associated



Fig. 8. Sections of 2 small pulmonary arteries. (Both stained by Elastic/Van Gieson, ×130.) *A*, Longitudinal section of artery showing recanalized thrombus. *B*, Transverse section of artery showing eccentric nodules of organized thrombus.

polycythemia.[2,3] The *small bronchial arteries*, easily recognized by their thick band of intimal longitudinal muscle, were unusually prominent in sections of the lung suggesting the development of a collateral bronchial circulation.

Sections of the lung were solid with blood due to the hemorrhage into the parenchyma. The liver showed pronounced fatty change as was evident from its macroscopic appearance. Finally, sections of the myocardium showed considerable areas of fibrosis possibly related to patchy coronary arterial ischemia brought about by small thromboses in the radicles of the coronary arterial tree due to polycythemia.

In summary, the appearances were those of pulmonary atresia with so-called coarctation of the pulmonary trunk. The associated diminution in pulmonary arterial pressure and flow had led to atrophic changes in the pulmonary trunk and widespread thrombosis in the pulmonary arteries. The inadequate blood supply to the lung had been alleviated by the previous performance of a systemic-pulmonary anastomosis and this had resulted in prolonged survival. There was also evidence of a collateral bronchial circulation. Death appears to have resulted from severe hemorrhage into the lungs. Patchy myocardial fibrosis appears to have followed focal coronary thrombosis also related to the polycythemia.

Diagnosis

Pulmonary atresia with coarctation of the pulmonary trunk. Widespread pulmonary arterial thrombosis. Surgical systemic pulmonary anastomosis and bronchial collateral circulation. Pulmonary hemorrhage.

REFERENCES

1. Heath, D., DuShane, J. W., Wood, E. H., and Edwards, J. E.: The structure of the pulmonary trunk at different ages and in cases of pulmonary hypertension and pulmonary stenosis, J. Path. Bact. 77:443, 1959.
2. Best, P. V., and Heath, D.: Pulmonary thrombosis in cyanotic congenital heart disease without pulmonary hypertension, J. Path. Bact. 75:281, 1958.
3. Heath, D., DuShane, J. W., Wood, E. H., and Edwards, J. E.: The aetiology of pulmonary thrombosis in cyanotic congenital heart disease with pulmonary stenosis, Thorax 13:213, 1958.

Use of phenylephrine in the detection of the opening snap of mitral stenosis

Morton E. Tavel, M.D.
William J. Faster, M.D. *
Charles Fisch, M.D. **
Indianapolis, Ind.

The importance of accurate detection of the opening snap in suspected or proved mitral stenosis hardly needs emphasis. In cases wherein the mitral stenosis is severe or is associated with tachycardia, however, the second sound to opening snap interval (2-OS) is often quite short and one may have difficulty in distinguishing the opening snap from normal splitting of the second heart sound. Moreover, in such situations as calcification of the mitral valve or congenital mitral stenosis an opening snap may be lacking. In many such cases, even phonocardiography may be of little assistance in ascertaining whether or not an opening snap is present. Because of these difficulties, we have turned to the use of a pharmacological agent that would delay the opening snap sufficiently to render it easily detectable. Phenylephrine, a sympathomimetic amine, displays such a property, and the purpose of this communication is to present this observation and to point out its potential clinical applicability. The results of this study have been mentioned briefly elsewhere.

Material and method

Twelve patients with mitral stenosis undergoing cardiac catheterization were selected for study. Of these 12 patients, there were 3 with pure mitral stenosis. Associated lesions occurred as follows: mitral insufficiency (4 cases), mitral insufficiency and aortic insufficiency (3 cases), mitral insufficiency and tricuspid insufficiency (2 cases). Three of these patients had pulmonary arterial pressures exceeding 50 mm. Hg systolic (Cases 3, 5, and 10).

The 2-OS interval represents the time between the beginning of the aortic second sound and the opening snap. In patients with atrial fibrillation, the interval used was the average of 10 consecutive cycles.

In order to assess further the effects of phenylephrine on the normal or widely split second sound, a control group consisted of 4 normal subjects, and another group consisted of 3 patients with atrial septal defect, ostium secundum in type, proved by cardiac catheterization.

Phonocardiography was performed with an Electronics for Medicine recorder

From the Department of Medicine, Indiana University School of Medicine and the Krannert Institute of Cardiology, Marion County General Hospital, Indianapolis, Ind.
Supported in part by the Herman C. Krannert Fund, United States Public Health Service Grants HE-4360, HTS-181, and HE-5749, the Indiana Heart Association.
*Assistant Professor of Medicine, Indiana University School of Medicine.
**Formerly Student Trainee, National Heart Institute.
***Professor of Medicine, Indiana University School of Medicine.

 February 1969 Vol. 77, No. 2, pp. 274-27[illegible]

Table I

Case No.	Diagnosis	Rhythm	2-OS interval (sec.)		Total amount of phenylephrine	Heart rate		Blood pressure		Phenylephrine effect on second heart sound
			Control	Phenylephrine		Control	Phenylephrine	Control	Phenylephrine	
1	Mitral stenosis	Atrial fibrillation	0.10	0.15	0.25	55	46	116/60	122/86	No change
2	Mitral stenosis	Regular sinus rhythm	0.08	0.12	0.25	82	58	96/60	106/80	No change
3	Mitral stenosis	Regular sinus rhythm	0.07	0.08	0.50	80	73	92/68	116/86	No change
4	Mitral stenosis and insufficiency	Atrial fibrillation	0.08	0.14	0.50	86	50*	130/80	160/90	No change
5	Mitral stenosis and insufficiency	Regular sinus rhythm	0.08	0.10	0.50	86	52	90/60	102/70	No change
6	Mitral stenosis and insufficiency	Atrial fibrillation	0.10	0.12	0.50	46	42	120/56	133/70	No change
7	Mitral stenosis and insufficiency	Atrial fibrillation	0.08	0.11	0.50	63	52	96/66	110/78	No change
8	Mitral stenosis and insufficiency aortic insufficiency	Regular sinus rhythm	0.08	0.13	0.80	88	46	120/60	160/90	No change
9	Mitral stenosis and insufficiency aortic insufficiency	Regular sinus rhythm	0.08	0.11	0.80	94	50	104/40	140/90	No change
10	Mitral stenosis and insufficiency aortic insufficiency	Regular sinus rhythm	0.04	0.07	0.25	84	53	120/80	158/80	No change
11	Mitral stenosis and insufficiency tricuspid insufficiency	Regular sinus rhythm	0.08	0.12	0.80	67	38	118/64	132/86	No change
12	Mitral stenosis and insufficiency tricuspid insufficiency	Atrial fibrillation	0.08	0.10	0.50	100*	80	102/80	102/80	No change
13	Normal	Regular sinus rhythm			0.8	67	37	106/64	124/94	No change
14	Normal	Regular sinus rhythm			0.5	58	36	110/48	125/60	No change
15	Normal	Regular sinus rhythm			0.25	72	43	130/70	150/90	From 0.03 to 0 sec.
16	Normal	Regular sinus rhythm			0.25	72	49	123/80	150/100	No change
17	Atrial septal defect	Regular sinus rhythm			0.8	89	40	104/46	124/72	No change
18	Atrial septal defect	Regular sinus rhythm			0.5	80	80	114/74	170/90	No change
19	Atrial septal defect	Regular sinus rhythm			0.5	66	52	108/66	175/94	From 0.05 to 0.08 sec.

*Average rate

model DR-8. Recordings were made with the use of a band pass filter set at 120 to 500 c.p.s. The filter slope was 6 DB/octave outside these limits. A paper speed of 100 mm. per second was employed and the interval between the time lines was 0.1 second. Microphones were placed at the lower left sternal border (fourth interspace) and apex for each tracing and the pulmonic area was chosen for recording when necessary to register the second sound components. The sounds were also monitored through the auditory outlet. Electrocardiographic standard Lead II was concomitantly used in all cases.

After a complete auscultatory and phonocardiographic evaluation a control tracing and blood pressure were taken. Following this procedure, 0.25 mg. of phenylephrine was injected intravenously. Phonocardiographic tracings were recorded for periods of 10 to 15 seconds at 15 second intervals. Tracings were taken with the patient in relaxed held expiration. Blood pressure determinations were taken approximately 10 seconds prior to each tracing. If the initial amount of phenylephrine failed to elicit bradycardia or a blood pressure rise of 15 mm. Hg or more systolic in approximately 2 to 3 minutes, subsequent injections of 0.25 mg. were administered and further tracings recorded. If headache or any other subjective discomfort appeared further doses were not given.

Results

The data are summarized in Table I and reveal that variable dosages of phenylephrine significantly and consistently prolong the 2-OS interval. Although the patient responses obtained were not in proportion to the various dosages given, the 2-OS interval was prolonged in every case from as little as 0.01 second to as much as 0.06 second (average 0.033 second). In Case 9 an opening snap was initially not clearly detectable but the delay brought

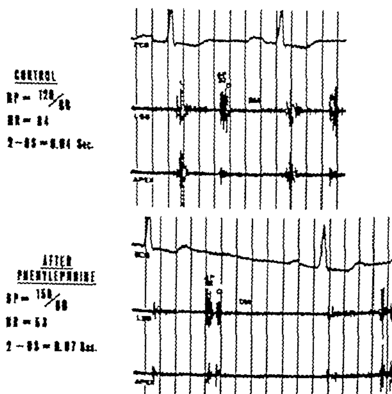


Fig. 1. Effect of phenylephrine on the 2-OS in mitral stenosis (Case 10) (Courtesy of Yearbook Medical Publishers, copyright, 1967).

out by phenylephrine allowed for easy identification (Fig 1)

On the other hand the normal subjects or patients with mitral stenosis showed little or no change in splitting of the second sound components in response to this drug (Figs. 1 and 2). One normal (Case 15) manifested a loss of splitting with phenylephrine after a control tracing indicated an interval of 0.03 second. One of the 3 patients (Case 19) with atrial septal defect showed considerable widening of the split with an increase from a control of 0.05 to 0.08 second after phenylephrine.

When the drug caused pronounced bradycardia and blood pressure rise the 2-OS interval generally was lengthened considerably. Conversely little change in heart rate and blood pressure resulted in relatively little effect on the 2-OS. In the 3 patients with atrial fibrillation phenylephrine caused a slowing of the heart rate and an average delay of the opening snap however we found that phenylephrine prolonged the 2-OS interval even in cycles having the same length as those found in the control tracing (Fig 3)

Side effects to phenylephrine were mild transient headaches and slight nervousness in 2 patients and precordial discomfort in one. The electrocardiographic pattern changed from regular sinoatrial rhythm to transient runs of ventricular bigeminy in 3 patients and runs of A-V junctional escape beats in one. These phenomena lasted 3 to 4 minutes in each patient, and disappeared spontaneously.

Discussion

Phenylephrine hydrochloride, a sympathomimetic amine raises blood pressure by causing peripheral arteriolar vasoconstriction and also induces a reflex bradycardia. Either elevation of systemic arterial pressure or prolongation of cardiac cycle length can prolong the 2-OS interval in mitral stenosis.[3,4] The heightened left ventricular pressure caused by phenyleph-

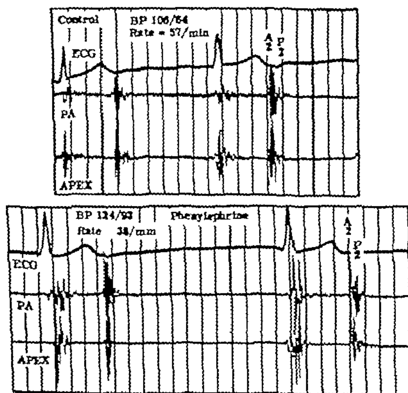


Fig. 2 Effect of phenylephrine on the normal second heart sound components (Case 13)

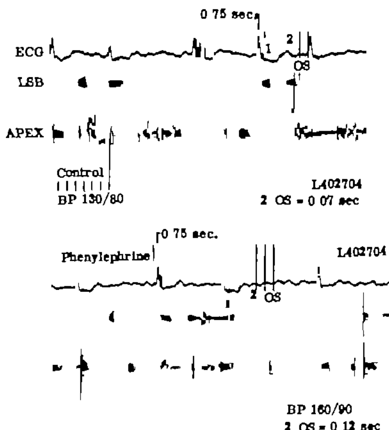


Fig. 3. Effect of phenylephrine in mitral stenosis with atrial fibrillation. After phenylephrine, the 2-OS interval lengthens considerably even in the beats following the cycles of identical length (0.75 second). (Case 4.)

rine requires a longer duration to fall to the level of left atrial pressure and thereby increases the time between aortic closure and the opening snap. In addition, the bradycardia, by allowing more time for left ventricular filling, probably allows the left atrial pressure to fall, providing an additional means to delay the opening snap.

Based on our findings, this drug should serve as a useful adjunct to the study of mitral stenosis. The failure to render a snap easily discernible despite a considerable change in blood pressure and pulse rate should militate *against* the presence of an opening snap in a given case. The implications of such a finding would in most cases, be that either the mitral valve is calcified and immobile or that mitral stenosis is not present. The presence of significant mitral insufficiency might theoretically offer an exception to the above rule, since phenylephrine would be expected to increase regurgitant flow and thereby raise left atrial pressure during ventricular systole. This could cause a compensatory shortening of the 2-OS interval. We did not encounter this problem despite the presence of some mitral insufficiency in 9 of our patients. Five of these latter (Cases 6, 7, 8, 9, and 12) were judged to have moderate to severe mitral insufficiency.

Splitting of the second heart sound was not increased in any of our normal subjects or in those with mitral stenosis when given phenylephrine, and this effect should enhance separation of the second sound components from the opening snap in order for the latter to be easily identified. One patient with atrial septal defect behaved in an opposite fashion, i.e., phenylephrine produced a significantly wider A_2 to P_2 interval. In atrial septal defect,

other investigators[4] have observed a dependency of the A_2 to P interval on cycle length. Castle[5] observed in a study of 41 cases, a significant tendency for splitting to be wider when the heart rate was slower Aygen and Braunwald noted in 4 cases of atrial septal defect with atrial fibrillation, that with longer cycles, the second sound would be split considerably more widely This increased splitting is probably explained by the fact that longer cycles will permit more atrial shunting with each beat and a greater disparity between the stroke volume of the 2 ventricles. On the other hand the second sound in the normal individual shows little or no tendency to widen at slower heart rates. Shah and Slodki, in a study of time intervals from the Q wave to the aortic and pulmonic components of the second heart sound found that as rate decreases there is a slightly greater increase in the interval from the Q wave to pulmonic closure interval than in that from the Q to aortic closure however their data indicates that the splitting interval should widen by *less* than 0.01 second even with great changes in rate. This is consistent with our observation that there was no significant change in the second sound splitting interval in the patients without atrial septal defect. The elevation of blood pressure caused by phenylephrine apparently had little or no effect on the splitting of the second sound and this observation agrees with that of Wallace and associates[8] who found that in the dog heart elevation of blood pressure had little or no effect on duration of left ventricular systole.

In conclusion, we feel that phenylephrine provides a relatively simple aid for assessing whether or not an opening snap is present in a given case The identification of such a sound is ordinarily reasonably diagnostic of mitral stenosis. For reasons mentioned above however this agent probably will not provide differentiation between the opening snap and the widely split second sound of atrial septal defect. Although the present study was a phonocardiographic one, we have often been able to appreciate these changes by auscultation thus suggesting the applicability of this test as a simple bedside maneuver

Summary

The effect of phenylephrine on the 2-OS interval in cases of mitral stenosis is described. This drug prolongs regularly the 2-OS interval and thereby facilitates recognition of the opening snap. By contrast, there was no significant change in the splitting of the second sound in normal subjects or in the patients with mitral stenosis, but of 3 patients with atrial septal defect, the drug caused considerable increase of the splitting interval in one. Because of the characteristic delay of the opening snap in response to phenylephrine, the use of this drug is potentially useful in identification of the opening snap particularly in situations where such a sound is confused with splitting of the second heart sound.

REFERENCES

1 T vel, M E. Clinical phonocardiography and external pulse recording Chicago, Ill., 1967 Yearbook Medical Publishers, p. 94.
2. Beck, W Schire, V Vogelpoel, L., Nellen, M., and Swanepoel, A. Hemodynamic effects of amyl nitrite and phenylephrine on the normal human circulation and their relation t changes in cardiac murmurs, Am. J Cardiol. 8:341 1961
3 Bayer O Loogen, F and Wolter H. H. The mitral opening snap in quantitative diagnosis of mitral stenosis, Am. Heart J 51:234, 1956.
4 Messer A. L., Counihan, T B., Rappaport, M D and Sprague, H B The effect of cycle length on the time of occurrence of the first heart sound and the opening snap in mitral stenosis, Circulation 4:576, 1951
5. Castle, R F Variables affecting the splitting of the second heart sound in atrial septal defect, Am Heart J 73:468, 1967
6. Aygen, M M and Braunwald, E. The splitting of the second heart sound in normal subjects and in patients with congenital heart disease, Circulation 25:328, 1962.
7 Shah P M and Slodki, S. J The Q-II interval A study of the second heart sound in normal adults nd in systemic hypertension, Circulation 29:551 1964.
8 Wallace, A. G., Mitchell, J H., Skinner S., and Sarnoff S. J Duration of the phases of left ventricular systole Circulation Res. 12:611 1963.

Anticoagulant therapy—Practical management

I. S. Wright, M.D.
New York, N. Y.

This year marks the thirtieth anniversary of the first administration of anticoagulants to a patient in the United States. Dr. Charles Best brought his supply of the available purified heparin from Toronto to New York and he and I administered this jointly to a patient who was suffering from intractable migratory thrombophlebitis of many months' duration. During the period of exploration, we have made or reviewed most of the possible mistakes and variations in the forms of anticoagulant therapy which have been in common use. There are two essential steps in treatment. The first is carefully selecting the patient who will receive it. The second is choosing the appropriate technique of administration, for anticoagulants can be satisfactorily administered by several techniques. Too frequently in clinical practice, the dosage has been either inadequate, inviting additional thromboembolic complications, or excessive, encouraging the development of hemorrhagic complications. Errors in dosage have been common in the case of individual patients, and have invalidated some large studies otherwise well designed to evaluate their use.

Like a football team, if the individual participants (in this case physicians) within a single institution use too many variations from a reasonably standardized procedure, the chance for error and complications increases. This article will deal primarily with the technique and practical aspects of anticoagulant therapy, but first some general statements must be made regarding selection of patients.

Selection of patients

The only logical reasons for the use of anticoagulant therapy are to prevent or to treat thromboembolic complications. Thromboembolism plays a major role in determining the degree of morbidity and the mortality of the majority of people who die in their middle or latter years.

Therefore, use anticoagulants to (1) prevent the formation of thrombi in conditions known to be favorable to their development, (2) permit the dissolution of sludge or early soft thrombus by allowing the fibrinolytic enzymes of the blood to become more active without the usual inhibiting forces, (3) prevent the mother clot, whether intracardial or intravascular, from propagation and embolization, and (4) discourage the propagation of clots within vessels from blocking off additional branches of these vessels.

The exact indications in terms of heart disease, cerebral vascular disease, peripheral arterial and venous disease, the problems of pulmonary embolism, and many other manifestations are not within the scope of this presentation. There are certain absolute contraindications, namely, the presence or immediate past history of severe hemorrhage, recent central nervous system surgery, hemorrhagic blood dis-

Emeritus Clinical Professor of Medicine, Cornell University Medical College, New York, N. Y.

cranias of significance, prostatectomy and pericarditis, but not including the friction rub associated with myocardial infarction. Relative contraindications suggesting a need for caution include a history of old gastrointestinal ulcers or colitis, now in active hypertension in excess of 180/110 polycythemia of a marked degree especially if hemorrhagic manifestations are significant, and the presence of renal or liver disease. Treatment with anticoagulants should never be considered as routine. Each case should be decided on the basis of the existing and probable indications and risks.

For example a slowly developing thrombophlebitis in the lower calf may usually be treated with oral anticoagulants. However if a patient has had one or more recent pulmonary emboli it is preferable to initiate the treatment with heparin changing to oral anticoagulants later after therapeutic activity has been achieved. With myocardial infarction there is a difference of opinion. Some physicians prefer to initiate treatment with heparin and at the same time start a coumarin. The heparin is then discontinued as the prothrombin time (activity) reaches a therapeutic level. Others are content for so-called good risk cases, to start with oral anticoagulants. In view of the difficulty in predicting which cases will develop further thromboembolic complications, the recommended procedure is to use heparin from the beginning.

With different thromboembolic cerebral vascular states there is also a justifiable modification in treatment. Heparin is recommended to initiate the treatment of patients with transient ischemic attacks or progressive strokes. With a cerebral embolus, where there is diapedesis and more edema, there is a greater tendency for hemorrhage (*in the brain tissue*). During the early hours after embolization therefore, it is considered wise not to use heparin but to wait for three or four days for stabilization of the local condition before the administration of oral anticoagulants.

The question of their use in the treatment of completed strokes is still subject to some difference of opinion and this controversy is not within the scope of this paper. If as the evidence suggests, they are to be used for the prevention of future thromboembolism oral anticoagulants are adequate.

In the presence of recurrent thromboembolism, decisions must be made about whether the treatment is to be short term or long term and if long-term how long. In some patients where repeated cessation of treatment has resulted in new thromboembolism they may be used for years.

Control and training

There is an absolute need for accuracy in detail. This therapy demands a disciplined experienced control. Unless a physician is prepared to deliver this type of service, he should request help from a trained team. Surveys have revealed that in hospitals where there is no well-organized anticoagulant team or where the physicians have no special interest in this therapy the therapeutic response has been unsatisfactory and the complication rate has been high. Correction of this situation results in marked reduction in the incidence of complications.

Studies reported by Dr. George Mayer of Queens University in Kingston Ontario revealed that when the physicians of that institution first started to use anticoagulants the incidence of error was considerably higher than later on in their training. When handled by inexperienced physicians four times as many errors were made in treatment of outpatients as in treatment of hospitalized patients. Such errors resulted in inefficiency of anticoagulant therapy when the house staff was beginning training. As their efficiency increased during five months, there was a 67 per cent decrease in errors in hospitalized patients and an 87 per cent decrease in errors in outpatients. The organization of an anticoagulant unit and the supervision by an expert permitted the detection and correction of 80 to 95 per cent of the potential errors. This confirms the general experience at the New York Hospital where a special team established the first anticoagulant clinic and has continued to provide a consultant service to the hospital staff. A meeting of the resident staff is held at the beginning of each new service year when certain guidelines are outlined for the techniques to be used. A liaison is then established between the anticoagulant service group who attend this session and the resident staff. This is necessitated by the fact that the resident staff come from many medical schools where

a variety of techniques are used. Regrettably, some arrive with no previous training in this field.

Selection and administration of the anticoagulant

There is now a considerable choice of anticoagulants which can be used. Heparin is most widely used as the parenteral anticoagulant, although warfarin may be used for this purpose. Heparin can be administered subcutaneously, intramuscularly, and intravenously. There have been preparations of long acting heparin for intramuscular use in which a variety of vehicles have been used.

Continuous intravenous heparin may be well controlled by the frequent use of Lee-White clotting time tests. This requires constant supervision as under postoperative situations. The long term use of intravenous heparin is not practical and indeed is subject to increasing error as the resident staff becomes fatigued with the supervision of the clotting time tests over a period of days. Subcutaneous or intramuscular injections of heparin sodium are now used more frequently. They are administered at intervals of six to eight hours and this usually proves to be satisfactory. The dosage depends in part on the acuteness of the situation. In general, the initial dose is 10 000 units of heparin sodium given subcutaneously. The clotting time should be tested before the first injection for control purposes and at the end of eight hours. The clotting time should return to about twice normal before administering a subsequent dose. The clotting time may reach twice normal at eight hours, ten hours, or twelve hours. This should be the guide for the timing of the next injection of 10,000 units. Once the time interval has been determined for a specific patient, it is not necessary to check the clotting time more than once a day before the administration of a subsequent dose. This method appears to be satisfactory and has been widely used in this country as well as in Europe.

There is a greater selection of oral anticoagulants. The first was Dicumarol. The initial or loading dose is 200 to 300 mg. The second dose, administered the next day, should be 150 mg and thereafter 50 or 75 mg may be given daily depending upon the prothrombin time. There are patients who require more or less than these suggested doses. The most widely used prothrombin time tests are based on the Quick one stage method. Although other tests have been advocated, the Quick test is satisfactory for practical use. The prothrombin time should be kept at about two times the normal control during the acute phases of the thromboembolic disease. For example, if the control time is 12 seconds the desired level should be 24 seconds, plus or minus 2 seconds. This results in a percentage of prothrombin activity of approximately 20 per cent. For long term therapy

Table I. Anticoagulant drugs for oral use

Drug	Loading dose (mg.) (First 24-48 hr.)	Maintenance dose (mg.)	Time to produce therapeutic levels (hr.)
Coumarin compounds			
Cyclocoumarol	125–200	12 5–50	36–72
Bishydroxycoumarin	200–300	25–150	36–72
Ethyl biscoumacetate	1 800–2 400	150–900	18–36
Nicoumalone	36–52	2–12	24–42
Phenprocoumon	18–30	0 75–6	30–48
Sodium warfarin	25–30	2 5–10	36–45
Indandione compounds			
Anisindione	800–900	75–100	36–60
Diphenadione	30–45	3–5	48–60
Phenindione	200–300	25–200	36–48

it is desirable that the prothrombin time be at a level approximating 1½ to 2 times normal.

Other oral anticoagulants which have been used widely both here and abroad include cyclocoumarol, bishydroxycoumarin, ethyl biscoumacetate, phenprocoumon, nicoumalone, and sodium warfarin. In the United States, sodium warfarin (Coumadin) is used most widely. The preferred loading dose is 25 to 30 mg, and the maintenance dose averages between 2.5 and 10 mg per day. The effort should be to keep the prothrombin time within the limits above mentioned. Some patients require only 2.5 mg every other day and others require much larger doses to secure adequate therapeutic levels. Indandione preparations have been used more widely in Europe than in this country. They have essentially the same action and effect on the prothrombin time, but reports suggest a greater incidence of hypersensitivity. They also color the urine orange so the ambulatory patient is less able to recognize minor urinary bleeding. Table 1 lists some statistics on the oral anticoagulants that are presently available.

Studies with other drugs include thrombolytic agents involving streptokinase and urokinase. More recently, the Maylayan pit viper venom (Fraction 6) (Arvin) has been studied in England. These agents are still experimental and are not yet ready for general clinical use. Although of great scientific interest, they will not be discussed further in this paper.

Interactions with other drugs

An important consideration in this therapy rests in the effect of other drugs used simultaneously upon the prothrombin time. This has been well summarized in the *Medical Letter on Drugs and Therapeutics* (Vol. 9, Dec. 1, 1967). Both potentiation and inhibition of anticoagulant activity has been encountered. Some drugs when used concurrently increase microsomal enzyme activity in the liver which in turn increase metabolic degradation of the coumarins. This reduces their anticoagulant effect. When such concurrent drugs are discontinued, one can expect an increase in the prothrombin time, sometimes to dangerous levels, unless the anticoagulant dosage is reduced. These drugs include phenobarbital, chloral hydrate, glutethimide (Doriden), meprobamate, griseofulvin and haloperidol (Haldol). Potentiating effects may also occur with drugs that inhibit the metabolic degradation of coumarins such as phenyramidol (Analexin). On the other hand, some drugs produce potentiating effects by displacing the anticoagulant from protein-binding sites in the plasma, thus increasing the peak concentration of free coumarins. These include phenylbutazone (Butazolidin), oxyphenbutazone (Tandearil), diphenylhydantoin (Dilantin) and the most commonly used salicylates.

Sulfisoxazole (Gantrisin and other brands), chloramphenicol (Chloromycetin), tetracyclines, neomycin and possibly other antibiotics may prolong prothrombin time in patients on oral anticoagulant drugs, mainly by interfering with vitamin K production by gut bacteria. Quinine, quinidine, norethandrolone (Nilevar) and dextrothyroxine (Choloxin) also increases the anticoagulant effects of coumarins, though the mechanisms are unclear.

Coumarins elevate serum concentrations of diphenylhydantoin, probably by inhibiting enzymatic degradation of diphenylhydantoin in the liver. Diphenylhydantoin toxicity has been reported in patients receiving both drugs. Coumarins also potentiate the hypoglycemic effect of tolbutamide (Orinase) apparently by inhibiting its conversion to carboxytolbutamide in the liver.

Recently, clofibrate (Atromid S) has been found to increase anticoagulant activity when it is added to a regimen already containing coumarin derivatives. We, therefore, suggest that when clofibrate is added to the regimen under such conditions, the coumarin should be reduced to approximately one third to one half of its former dosage, and the prothrombin time checked frequently. The coumarin may then be gradually increased toward its former dosage. It will usually require a lower dosage than before the administration of clofibrate to produce optimal therapeutic response. The actions that are described above are reversed when these drugs are discontinued and it is essential to readjust the anticoagulant dosage accordingly.

Hospital orders

The manner in which the orders are written is of importance It is advisable to require on or near the front of each hospital chart an anticoagulant sheet which specifically requires the daily entry of the prothrombin time of the patient the control prothrombin time for that day and the dosage of the drug administered It is thereby easily possible to note the trends of the response and take appropriate steps before extreme situations arise If there is a prolongation of the prothrombin time above the optimal therapeutic level it is wise to decrease the dose of the anticoagulant. On the other hand if it seems to be shortening significantly the indication for increasing the dose is clear

Additional tests for control

Various tests are used in addition to the Quick one stage test and its modifications and a wide variety of thromboplastins are available. These thromboplastins vary greatly in strength and action without adding significantly to the effectiveness or safety of the therapy The loyalty of various workers to the tests they have developed or used has proved to be a major handicap in the standardization of anticoagulant therapy on a national or international basis. The International Committee on Thrombosis and Hemostasis is endeavoring to select a thromboplastin which will be adopted as an international standard

One example of the problem is presented by the Thrombotest (Owren of Norway) which requires that a lower level of activity (8 to 10 per cent) be adopted as the optimal therapeutic level of activity as compared with 20 to 25 per cent. Lack of understanding of this fact has confused clinicians and invalidated some large scale studies.

When the Thrombotest indicates a level below five per cent it does not indicate how far below five per cent it may be. Thus it fails to indicate how much vitamin K_1 one should give as an antidote Otherwise, we have found it to be satisfactory It may be used both as a finger puncture test and a vein test which is advantageous.

Whatever thromboplastin is used whether it be Permaplastin Simplastin Acuplastin or a local brain thromboplastin product, it is essential that the physician clearly understand the action of that particular thromboplastin in terms of therapy for his patient He must become acquainted with the values of the prothrombin times or percentage activity which are optimal and not dangerous as reported in his own hospital or geographical area. This requires evaluation of the performance of the laboratory responsible for the data.

Antidotes

For an antidote to excessive oral anticoagulant use vitamin K_1 This is usually administered in dosages of 5 mg or less. Oral administration is usually satisfactory since it acts within three to six hours, almost as rapidly as intravenous administration. It is rarely necessary to use larger dosages. If the patient is hemorrhaging briskly 10 mg may be given followed by an additional 5 mg in a few hours if the prothrombin time does not return toward normal. When the therapy is controlled by physicians who are experienced with its use, serious hemorrhages are very rare. The causes of unpredictable hemorrhage include unrecognized ulcers unrecognized cancer of the gastrointestinal urological or respiratory tracts, or the result of an accident or injury There have been numerous uses in which this has led to the discovery of a previously undiagnosed lesion.

Whole blood transfusions may be given for massive hemorrhage, but at the New York Hospital these have rarely been necessary in recent years.

When the prothrombin time reaches a level of 45 or 50 seconds against a control of 12 to 15 seconds, even in the absence of bleeding it is advisable to give 5 mg of vitamin K_1 and to omit a dose or two of the anticoagulant. This in a sense acts as a buffer preventing the prothrombin time from becoming excessive, and thereby decreasing the risk of bleeding

Heparin rarely requires an antidote because its action is fairly short-lived, but if necessary protamine sulfate, milligram for milligram may be used This is rarely necessary

Hospital protocol

It is essential that these patients be observed daily The blood sample should be taken each morning and the prothrombin

time reported by noon time. This should be checked by the physician or nurse prior to the administration of the daily dose at approximately 6 P.M.

An example of a useful schedule is as follows

First day Coumadin (warfarin sodium) 25 mg second day 15 mg third day 5 mg thereafter 5 mg daily unless the prothrombin time exceeds 25 seconds (with a control time of 12 to 14) This provides an automatic cut-off If the prothrombin time exceeds 25 seconds, the nurse does not administer the daily dose pending review by the physician. Extensive experience has shown this to be a safe procedure It has been proven that more errors can occur if the dosage is ordered each day The attending physicians or even the resident may fail to check the prothrombin time occasionally and a dose may be omitted This is a common error in many hospitals If the prothrombin time is less than one and one half times the control time, the dosage should be increased appropriately

The ambulatory patient

In preparation for discharge the patient must be carefully instructed regarding the dose of anticoagulant he is to take each day until he is to see his physician. This must be written out or provided in chart form so that there is no chance of error It has been found that it is better to use a standard dosage strength for a given drug For example, in the use of warfarin sodium we only use 5 mg. tablets. The use of 2 5 mg 7.5 mg and 10 mg tablets tends to confuse the patient as to which tablet he has taken and in telephone conversations he may make an error in trying to tell his physician. If a 5 mg. tablet is used he may be instructed to cut it in half or take two tablets. Both the patient and the physician should know precisely the dose taken After discharge the patient should have a prothrombin time test within three or four days, then once a week if he seems to be well controlled This may continue on a weekly basis for several weeks, and ultimately perhaps extend to two or even three weeks. Longer intervals between tests are not recommended although the drug remains standardized the condition of the patient may not. Infections, diarrhea alcoholic binges lack of food and as previously discussed various medications may influence the prothrombin time Each patient should carry a card stating that he is on anticoagulant therapy and the name address and telephone number of his physician Suitable cards are available from the American Heart Association

Duration of treatment

The question as to how long patients should be treated depends upon the condition under treatment. A patient with a simple thrombophlebitis which subsides readily should be on anticoagulants for a month or six weeks. Short periods of treatment (a week or less) are frequently followed by a relapse sometimes with serious pulmonary emboli On the other hand the patients who have recurrent thromboembolism such as pulmonary emboli transient ischemic attacks, or myocardial infarctions, may be carried for many months or even years. There are now patients who have been on anticoagulant therapy for more than twenty years without any evidence of liver renal or other complications as a result of their anticoagulant therapy The risk of serious hemorrhage must be weighed against the risk of the thromboembolic disease of the patient Inadequate therapy cannot be expected to produce satisfactory results

REFERENCES

1 British Medical Research Council An assessment of long-term anticoagulant administration after cardiac infarction, Second Report, Brit. M J 2:837 1964
2 Douglas, A S. Anticoagulant therapy Oxford, 1962, Blackwell Scientific Publications
3 Fischer S P thology of coronary occlusion with special reference to anticoagulation medication, Copenhagen, 1963, Store Nordiske Videnskabsboghandel.
4 Friedberg, C Anticoagulant therapy Heart Bulletin 17:27 33, 40 March-April, 1968
5 Interactions of or l anticoagulants with other drugs, M Letter Drugs & Therapeutics 9 Dec 1 1967
6 Loeliger E A Hensen, A Kroes, F Van-Dijk, L M Fekkes, N De Jonge, H nd Hemker H C A double blind trial of long term anticoagulant treatment after myocardial infarction, Acta med. scandinav 182:549 1967
7 Mayer A. Training and experience of physicians in the management of adequate anticoagulant therapy Canad M A. J 92 182, 1965.
8. Nichol, E. S. Anticoagulant therapy in ischemic

heart disease, Internat. Symposium, New York, 1964 Grune & Stratton, Inc.
9. U. S. Veterans Administration study Ebert R. V. Chairman Long-term anticoagulant therapy after myocardial infarction, J. A. M. A. 193:929 1965
10. Vigran, I. M. Clinical anticoagulant therapy Philadelphia, 1965 Lea & Febiger Publishers.
11. Wright, I. S. A critical appraisal of anticoagulant therapy presented before Forty-sixth South African M. Cong. Durban, July 21 1967 South African M. J. 42 August 1968
12. Wright, I. S. A history of anticoagulants, Symposium, Circulation 19 110 1959
13. Wright, I. S., Marple, C., and Beck, D. F. Myocardial infarction, report of the Anticoagulant Committee of the Am. Heart A., New York, 1954 Grune & Stratton, Inc.
14. Wright, I. S.: Strokes—diagnosis and modern treatment (I). Mod. Concepts Cardiovas. Dis. 34:31 July 1965.
15. Wright, I. S. Strokes—diagnosis and modern treatment. II Mod. Concepts Cardiovas. Dis. 34:35 August, 1965.
16. Wright, I. S. Strokes—diagnosis and modern treatment. III Mod. Concepts Cardiovas. Dis. 34:41 September 1965

Annotations

The effect of transbrachial retrograde left heart catheterization upon cardiac output

The physiologic effects of left heart catheterization by transbronchial left atrial puncture, posterior percutaneous left atrial puncture, and transseptal left atrial puncture have been described. Although the retrograde approach to the left heart is probably the one most commonly used today few data are available regarding the physiologic effects of this procedure itself. We therefore, carried out a study on 50 patients to determine the effects of transbrachial retrograde left heart catheterization upon indicator-dilution cardiac output determinations.

These patients, with various forms of arteriosclerotic, rheumatic and myocardial disease, including seven with normal hemodynamics, were studied by cutdown in the right upper extremity. The pulmonary artery (PA) was catheterized by standard technique, and an indwelling arterial needle was inserted into the left femoral artery (LFA). Two control cardiac output determinations were then recorded with injections of indocyanine green dye into the PA with sampling from the LFA. These were recorded and analyzed by previously described techniques.

A brachial arteriotomy was then performed, and with either a No. 7 angiography or No. 8 coronary arteriography catheter the aorta and then the left ventricle (LV) was catheterized. After simultaneous LV and LFA pressures and LV end-diastolic pressures were recorded, two dye curves were again inscribed from PA to LFA to measure cardiac output.

When we compared the mean cardiac index determinations before (2.52 ± 0.07 S.E.M. liters per minute per square meter) and after (2.49 ± 0.07 S.E.M. liters per minute per square meter), retrograde LV catheterization, no significant difference was found ($0.8 > P > 0.7$). The postretrograde dye curves were recorded 5.0 ± 0.5 S.E.M. minutes after the catheter entered the LV.

Therefore, as previously shown for transseptal left atrial puncture, transbrachial retrograde LV catheterization does not disturb the basal state, and valid hemodynamic measurements may be recorded within five minutes of entering the LV. Since these two techniques, alone, or simultaneously are the methods most commonly used to record left heart hemodynamics, various physiologic measurements and interventions may be carried out with confidence with either approach.

Joseph W. Linhart, M.D.
Frank J. Hildner, M.D.
S. Serge Barold, M.B., B.S., M.R.A.C.P.
Philip Samet, M.D.
Division of Cardiology, Department of Medicine
Mount Sinai Hospital
Miami Beach, Fla.
Department of Medicine
University of Miami School of Medicine
Coral Gables, Fla.

REFERENCES

1. Morrow, A. G., Braunwald, E., and Tanenbaum, H. L.: Transbronchial left heart catheterization: A modified technique and its physiologic evaluation, S. Forum 8:390, 1957.
2. Samet, P., Bernstein, W. H., Litwak, R. S., Turkin, H., and Silverman, L.: Steady-state cardiac output determination during combined right and left heart catheterization, Circulation 18:60, 1958.
3. Samet, P., Bernstein, W. H., and Medow, A.: Effect of transseptal left atrial puncture upon cardiac output, Circulation 30:188, 1964.
4. Hildner, F. J., Drake, E. H., Gale, H. H., and Ormond, R. S.: Transbrachial retrograde left heart catheterization. Evaluation of 600 consecutive cases in adults, Am. J. Cardiol. 18:52, 1966.
5. Samet, P., and Bernstein, W. H.: Methodology of indicator dilution cardiac output determination, Dis. Chest 50:362, 1966.

The cardiologist, nurse, and nursing

Despite many important technologic advances in diagnosis and management of patients with heart disease, elegant bedside nursing remains foremost in importance in the care of the patient. The person constantly at the bedside is the nurse who assists the cardiologist. Unfortunately, the cardiologist fails to realize that he is primarily responsible for the entire care of the patient, including nursing. A good nurse assures effective therapy, proper administration of drugs, rest, comfort, and satisfaction to the sick patient. For good nursing care there must be enough nurses who are well educated, intelligent, sound in judgment, dedicated, and highly motivated. They must be excellently trained. To be most effective they should have an excellent family background. All these requisites tend to assure the proper type of personality for kind, considerate, and sympathetic nursing.

The nurse-patient ratio should be adequate and suitable to meet the demands and severity of the sickness. It is humanly impossible for one nurse to render acceptable care of more than four moderately sick patients or more than one severely sick patient. One nurse per patient is ideal because a patient with heart disease who requires hospitalization is usually very sick. At present, adequate nurse-patient ratio is usually demanded only for intensive care units, postoperative recovery rooms, and special research wards. The general wards of the hospitals and even private rooms usually lack this ideal ratio. This is particularly true of the large hospitals where the nurse-patient ratio is far from ideal so that the care of the cardiac patient remains unsatisfactory and inadequate. Inadequate nursing results in confusion, slow recovery of the patients, serious errors in management, and prolonged hospitalization. Occasionally the quality of the nursing can even mean the difference between recovery and death.

It must be clearly understood that mere production of nurses will not assure ideal nursing care and excellent management. It should be remembered that it is the cardiologist who is responsible for the entire management of the patient, including the performance of the nurse. The nurse at the bedside is regularly confronted with important problems in cardiac diseases which require immediate decisions. She must know how to act in an emergency, when to secure the cardiologist's help, and when and how to use her own initiative, knowledge, and judgment. She must never guess the answer to a problem. Mere passing of examinations and display of a certificate should never be considered as evidence of a good nurse. Kindness, sympathetic personality, skilled pair of hands, and mature competence are far more important than degree or certificate. A nursing *Tiemert* once wrote, "*Pair of hands* is a phrase generally used in pejorative sense in the nursing world. Despite the advances of a technological age, it is so often by her hand that the nurse can communicate. By her hand the nurse can communicate her training. Her hands must be active, carrying tasks with deftness and skill; her hands may be quiet and tranquil, while she listens to anxieties that so often disturb the patient as much as his physical illness—without willing hands, be they active in practical skills or passive in the reception of confidence, nursing must prove ..."

During the training and education of the nurse one must inculcate in them a sense of responsibility and dedication both as professional women and responsible citizens. The physician and the nurse must consider the patient first at all times. Nurses should be constantly reminded to observe the three aspects of human life—body, mind, and spirit, which are all altered in disease.

The art of communication is another aspect often neglected during training. A nurse should communicate properly not only with the cardiologist and the cardiac patient but also with the family. During illness both the patient and his family are anxious, are greatly disturbed emotionally, feel highly inadequate, are dependent and extremely inquisitive, and can be disturbing to effective cardiac care. Poor communication is frequently responsible for the remark that nurses are so good with the patient and bad with the people. Besides dedication and patience it should be stressed to the nurse that the basis of effective communication is humility and excellent judgment. The nurse must not only know what to say but, equally important, what not to say to the patient and each person who visits the patient, for individuals of the family and friends vary considerably. She must "protect" the patient from all visitors, family included, until the patient has convalesced sufficiently.

One of the shortcomings of modern nursing is the indiscriminate tendency to employ new developments and yesterday's discoveries instead of improving well-accepted methods and practices. When they adopt such an "ultramodern" attitude, nurses frequently behave as poor doctors rather than as excellent nurses.

Finally, a word about the cardiologist-nurse relationship is not only in order but extremely important. This relationship is almost always neglected. The cardiologist and nurse should work together towards a common goal—the care and recovery of the sick. This obviously requires utmost cooperation and coordination between the two. A cooperative effort cannot be overemphasized in the care of the patient with serious and advanced heart disease. Sudden and unexpected death is forever possible and often probable. Hence, meeting of the physician initially with each nurse to explain his patient's illness, personal peculiarities, the objectives in therapy, and expectations from her nursing effort is necessary for effective nursing. The usual trend in general hospital practice is to bid the nurse the time of day, ask a few questions about the patient, issue a few orders, and quickly escape from the bedside—and then to blame the nurse for all errors and unfavorable reactions and results. This kind of practice is not only un...

to the nurse but can be harmf l to the patient and reflects poor practice of medicine. On the other hand, the physician should carefully and critically observe the quality of the nursing care should judge the nurse personality bility and interest, and should decide t the outset whether or not she is suitable for the particular patient. Every nurse will not be suitable for the care of all cardiac patients. The nurse must be selected t fit the personality and needs of the patient. Any other considerations will merely represent compromises, which can mean the difference between recovery and death. The nurse notes must be read routinely nd also judged for accuracy. Only accurate, reliable obser vations, data, and notes are to be tolerated. The nurse must be questioned bout the progress of the illness and the patients needs. Her judgment and performance must be regularly observed. She must be considered nd treated as collaborator in an important effort and responsibil ty—the management of cardia patients. This aspect of the cardiac care is too often neglected, ignored and not f lly ppreciated. The value of elegant, effective bedside cardiac nursing can be neither overemphasized nor compromised.

A good nurse predisposes to good patient care.

G E. B rch, M.D
Asam Ansa i, M.D
Department of Medicine
Tulane School of Medicine
New Orleans La 70112

REFERENCES

1. Editorial Nursing times Fri May 7 1965 Published by Macmillan (Journals) Ltd.
2. Burch, G. E., and Ansari, A. Bed rest, diet nursing and environment, AM. HEART J 77 1 1969

Does morphine deserve a primary role in coronary care therapy?

At the present time, there is still significant mortality rate from recognized transmural myocardial infarction. Including both early and posthospital admission deaths this rate has been est mated at approximately 45 per cent. Even ith optimum coronary care in general hospital setting the mortality rat from transmural myocardial infarction is 25 per cent.

The primary treatment for acute cardiac ischemia involves the administration of morphine or other algesic. I this pplication, morphine has several relevant pharmacologic effects For example, it decreases heart rate dilates peripheral nd coronary essels, and constricts abdominal isceral essels. There is some indication that it lso acts to mobilize blood from the pulmonary circulation t the venous system, thereby relieving pulmonary edema. I addition, morphine is sedative, muscle relaxant, and respiratory depressant. However the most significant effect of morphine is to bolish or t least markedly diminish the pain associated w th the infarction, and, in this respect, it is extremely effective agent.

I general, the patient who enters hospital coronary care unit will be given enough morphine or similar agent to relieve his pain. Several hours later should the pain recur further analgesic may be provided and the pattern of administration may be on 3 to 4 hourly basis. During this time the patient may ha perfectly normal vital signs, ith pulse rate of perhaps 85 or 90 and blood pressure of 120/80. Because of this nd lso because the recurring pain is promptly relieved by ppropriate analgesic agent, the personnel withi the coronary care unit belie that the situation is essentially under control.

However as is generally believed to be th case the pain of myocardial infarction is, in some more-or less linear fashion, related to the degree of coronary ischemia The patient who has had an infarc tion of limited area of his myocardium will usually experience less pain tha the patient who sustains an extensive infarction. From the previous discussion, t would seem likely that, during the time when his vital signs are perfectly normal and his electrocardiogram perhaps only slightly abnormal, the patient may be sustaining progressively more inf rction of his myocardium H may enter the coronary care nit with myocardium that is still 90 per cent functional, but, over the next several hours some degree of this muscle mass may be lost through coronary ischemia and necrosis. Progressively as the hours pass, the amount of viable myocardium may decrease to 80 per cent, then 70 per cent then 60 per cent, and, perhaps, 50 per cent. During all of this time, the patient vital signs may continue to be relatively normal for tw reasons (1) There is initially some reserv myocardial capacity which—especially in younger individuals—may be substantial. In such cases, even the continual monitoring of cardiac output may be deceptive, as this parameter may also be normal throughout fairly extensive infarction. (2) There is peripheral vasoconstriction which once significa t infarction has occurred, tends to maintain sy temic arterial pressures in the face of falling cardiac output The maintenance of normal blood pressures is lso supported by the fact that th patient remains on complete bedrest, so that heart ith essentially no reserve myocardial capacity can provide adequate pump function.

After enough myocardium has necrosed perhaps

6 to 24 hours after the patient entered the coronary care unit, there may be a fairly abrupt fall in blood pressure a rise in the pulse rate, and the development of clinically evident shock. This may ll occur rather suddenly since left ventricular myocardium which falls behind in its pump function by as l ttle as 1 ml per troke can lead to a pulmonary ccumulation of two liters in as little as fifteen minutes. This is usually a particularly critical moment in the patient course and, as has been hown by Griffith prompt and igorous treatme t is mandatory However cardiogenic shock is a lethal condition and as has bee indicated by Reeves "The mortality rate of cardiogenic shock varies with the rigorousness of ts d finition rather than with the pressor substance used n ts treatment

The unfort nate fact about the above all-too-frequently encountered situation is that the alarm i not sounded soon enough Wh le the patient ma not die of cardiogenic shock u til his blood pressure falls his myocardium is likely to be dying (or necrosing) throughout his ta in the coronary care unit. During this time his only therapy may be morphine (or other analgesic), which— add tion to having certain beneficial effects—is also responsible for masking' the patie t progress ve infar tion One would not consider administering analgesia as the treatment of chon n bowel inf rction. It is believed that the same principle should in some fashion be pplied t myocard al nfarctio as well

What is proposed is that a new look be taken t th use of analgesia in the corona y care unit and that other gents such as the mor potent vasodilators nd peripheral vasoconstrictors, be utilized as the treatment for *contin g* myocardial infarc tion pain, even n the face of normal vital signs. As newer devices for ugmenting coronary circulation, such as balloon pumps,[8,9] become vailable the time to use such devices may be in the presence of continuing infarction pain. At present such devices are utilized only after the patient has been in cardiogenic shock for several hours at which time too much myocardium may already be necrosed to perm t the salvage of patient with reasonably functional circulatory capacity Continued attempts directed toward the treatment of myocardial infarction shock, through medical or surgical means, are not likely to be particularly successful early because too much myocardium may have necrosed by the time this stage is reached. Even on a theoretical basis, the only therapeutic approach that appears to make any sense is that directed at the myocardium at a time when it is still 60 to 70 per cent functional. W should not stand idly by administering morphine, as the myocardial fact. dwindles to the 20 to 30 per cent range, and the patient abruptly becomes hypotensive, develops myocardial infarction shock, and dies.

Philip I. Hershberg, M.D.
Lahey Clinic Foundation
Boston, Mass.

RFFERENCES

1 Hershberg, P Unpublished data
2. Grace, W J Mortality rate from acute myocardial infarction, Am. J Cardiol. 20:306, 1967
3 Friedberg, C. K. Diseases of the heart, ed 2, Philadelphia, 1956 W B. Saunders Company, p. 362.
4 Beckman, H. Pharmacology the nature, action, and use of drugs, Philadelphia, 1961, W B. Saunder Company p. 228.
5 Henney R. P Vasko, J S., Brawley, R. K., Oldham, H N and Morrow A. G Effect of morphine on resistance and capacitance vessels of peripheral circulation, Am. Heart J 72:242, 1966
6. Griffith, G. C. The treatment of shock associated with myocardial infarction, Circulation 9:527 1954
7 Reeves, T J Year book of medicine, Chicago, 1967 Year Book Medical Publishers, Inc., p. 256
8. Laird, J D Jones, R. T Austen, G and Buckley M. Observations of the dynamics of an intra-aortic balloon pump, Dig. of the 7th Internat. Conf. on Med. and Biol Engineering Stockholm, 1967 Langlofs Lith. p. 382.
9 Kantrowitz, A., Tjonneland, S., Freed, P S., Phillips, S. J Butner A. N and Sherman J L. I itial clinical experience with intra-aortic balloon pumping in cardiogenic shock, J.A.M.A. 203 113, 1968.

Incidence and management of supraventricular arrhythmias after acute myocardial infarction

Continuous electrocardiographic monitoring has revealed a high frequency of all cardiac arrhythmias after acute myocardial infarction. Formerly supra ventricular rrhythmias were detected in only 10 to 15 per cent of patients.[1-4] With continuous monitoring they ha e been detected in 20 to 30 per cent.[4-] Such arrhythmias include trial fibrillation, atrial flutter paroxysmal trial tachycardia, and atrioventricular nodal rhythm

The success of D C. reversion therapy has influenced the treatment of all cardiac arrhythmias W describe here our experience in the manage

ment of supraventricular arrhythmias after acute myocardial infarction, with particular reference to the value of D.C. reversion.

A total of 222 patients with proved recent myocardial infarcts admitted to the coronary-care unit of King' College Hospital (London) between December 1965 and August, 1967 were included.

The patients were admitted through busy accident service within 24 hours of the development of symptoms, the mean delay being seven hours six minutes. All patients underwent continuous ECG monitoring for t least 72 hours.

Of the 222 patients, 170 were men and 52 were omen. Their ages ranged from 37 to 82 years, the average age being 57. The first 114 patients included in this report also formed the clinical material for a double-blind trial of prophylactic oral propranolol in dose of 20 mg. every six hours for 28 days[6]; 56 patients received propranolol in this dosage.

Of the 222 patients, 54 died during the first 28 days after the acute episode of infarction—a mortality rate of 24.3 per cent. I 73 per cent of the patients there was some disturbance of rate rhythm, or conduction. In 90 patients (40 per cent), one or more serious arrhythmias developed, including trial tachycardia fibrillation or flutter trioventricular nodal rhythm entricular tachycardia or fibrillation, nd advanced degrees of trioventricular block. The incidence of cardiac arrhythmias is presented in Table I.

Supra entricular arrhythmias developed in 46 patients (21 per cent). All but one ppeared within the first 72 hours after the nfarct. I 5 cases, recurrent episodes were noted later in the hospital tay. In 34 of the 46 patients with supraventricular arrhythmias, the site of infarction was anterior in 9 of these, the serial ECG s subsequently showed evidence of lateral extension.

Transient supraventricular arrhythmias, usually atrial fibrillation or nonparoxysmal nodal rhythm were noted in 13 of our patients and were not hemodynamically significant. The reports of Julian and associates[4] and Fluck and associates[8] include similar patients. However in 17 patients with atrial fibrillation, 13 with atrial tachycardia, 2 with trial flutter and 1 with nodal rhythm the arrhythmia was more persistent nd associated with a rapid ventricular rate. These patients developed heart failure hypotension, or shock. The significant hemodynamic deterioration which may be associated with supra entricular tachycardias and rapid ventricular rates was demonstrated by Corday and associates[10] in 1959. Sustained supraventricular arrhythmias resulting from cardiac infarction are by no means benign and may constitute critical hazard.

I the past, trial tachycardia has been regarded as ncommon arrhythmia fter acute myocardial infarction, unless digitalis toxicity is the cause. However 15 of our patients had trial tachycardia and in only 2 instances was digitalis a possible cause. Earlier failure to recognize the frequency of this arrhythmia may have resulted from the overdiagnosis of entricular tachycardia since in standard monitoring leads trial activity is frequently obscure particularly when tachycardia is associated with aberration of the QRS complexes. Esophageal leads were used to clarify the diagnosis

Table I. Incidence of arrhythmias in 222 patients with acute myocardial infarction

Arrhythmia	Incidence	Mortality rate (per cent)	ECG site of infarction			
			Anterior	Posterior	Anterior and posterior	Undetermined
Sinus tachycardia (>100 per minute)	73	52	39	20	12	2
Sinus bradycardia (<60 per minute)	65	11	29	31	5	0
Supraventricular extrasystoles	32	16	21	10	1	0
Ventricular extrasystoles	75	4	41	24	8	2
Atrial tachycardia	15	27	12	2	1	0
Atrial flutter	2	0	2	0	0	0
Atrial fibrillation	24	29	17	6	1	0
Nodal rhythm	5	0	3	2	0	0
Ventricular tachycardia	14	43	9	4	1	0
Ventricular fibrillation	21	52	14	7	0	0
First degree trioventricular block	23	44	10	12	1	0
Second degree trioventricular block	8	25	1	7	0	0
Complete heart block	11	64	5	5	1	0
Bundle branch block	22	36	8	6	1	7

Table II Management of supraventricular arrhythmias

Arrhythmia	*No. of patients*	*Treatment**					*Returned to sinus rhythm*	*Deaths*
		None	*Digitalis*	*Propranolol*	*Propranolol and digitalis*	*D.C. countershock*		
Atrial tachycardia	15	2 (2)	6 (1)	3 (2)	3 (0)	11 (9)	11	1
Atrial fibrillation	24	7 (3)	12 (4)	3 (0)	2 (0)	7 (3)	11	1
Atrial flutter	2	0	0	0	0	2 (2)	2	1
Nodal rhythm	5	4 (4)	0	0	0	1 (1)	5	4

*The figures in parentheses indicate the number of patients in each treatment group who reverted to sinus rhythm.

in 3 of our patients however by means of an electrode in the passage of an esophageal tube. We now use a percutaneous right atrial lead.[28]

Specific therapy was employed in patients with supraventricular arrhythmias whenever the ventricular rate was persistently over 100 per minute and associated with the development of heart failure, hypotension, or shock. The specific management of individual arrhythmias in our patients is illustrated in Table II.

Digitalis preparations were used initially unless the deterioration was so critical as to demand immediate reversion to sinus rhythm. They successfully controlled the ventricular rate and were associated with return to stable sinus rhythm in 4 patients with atrial fibrillation and 1 with atrial tachycardia.

In 23 episodes of supraventricular arrhythmia in 21 patients hemodynamic deterioration was so severe that emergency D.C. reversion was attempted. In 19 episodes, reversion to sinus rhythm occurred with satisfactory immediate improvement in the hemodynamic situation. In 12 of the 14 patients with atrial tachycardia, atrial flutter, or nodal tachycardia treated with D.C. shock, successful reversion to sinus rhythm was achieved. Recurrences in 2 patients more than 24 hours later were also reverted with D.C. shock, but in a further patient recurrence 4 days after the initial episode proved fatal. In these patients with atrial tachycardia, flutter, or nodal tachycardia, D.C. reversion was usually dramatically successful and we feel it is the treatment of choice when persistent rapid rate is associated with hemodynamic deterioration.

In contrast, of 7 patients with atrial fibrillation treated with D.C. shock, 2 failed to revert completely, 2 were associated with initial reversion to sinus rhythm but atrial fibrillation recurred within a few hours and 1 patient who was reverted to sinus rhythm developed a fatal cerebral embolus 48 hours later while still in sinus rhythm and despite anticoagulants. Only 2 patients with atrial fibrillation were reverted to stable sinus with D.C. shock. In review of the 24 patients with atrial fibrillation in this series we now conclude that when the arrhythmia is persistent and associated with a rapid ventricular rate and hemodynamic deterioration, digitalization is the treatment of choice. D.C. shock will rarely be indicated in this situation.

We noted that successful reversion to sinus rhythm in supraventricular tachycardias after infarction was usually achieved with D.C. discharges whose total energy level was less than 50 watt-seconds. When higher energy levels were required, D.C. reversion failed.

Patients who urgently require D.C. reversion for a supraventricular arrhythmia after infarction but have already been receiving digitalis preparations constitute a special problem. Careful attention to potassium replacement, particularly when diuretics are in use, limits the number of patients developing digitalis-induced arrhythmias. The problem of serious postreversion arrhythmias in the presence of digitalis remains. We agree with Lown and co-workers[29] that in the early stages after acute infarction it is preferable to use intravenous ouabain to control heart failure, and ventricular rates in supraventricular arrhythmias; the regulation of dosage is easier and the rapidity of elimination of the drug makes potential hazard less of a hazard. In addition, our own experience after acute infarction and Kleiger and Lown's[30] earlier report on postcardioversion arrhythmias in digitalized patients with atrial fibrillation lead us to suggest that, when D.C. shock is required, low energy discharges beginning at 50 watt-seconds with the electrodes in anterior and posterior positions are preferable.

Propranolol was successful in reverting to sinus rhythm two patients with atrial tachycardia, one of whom prior D.C. shock had been unsuccessful. As we[31] have previously reported, propranolol given prophylactically by the oral route does not influence the frequency of supraventricular arrhythmia after acute infarction. Attempts to suppress frequent supraventricular extrasystoles with continuous lignocaine infusions were not successful.

The mortality rate of 24 per cent in patients with supraventricular arrhythmia is strictly comparable to the over-all figure in our group of patients. This was also the experience of Julian and colleagues. In contrast, Stock and colleagues

Australia found a mortality rate of 53 per cent in patients with supraventricular arrhythmias, which was higher than the 30 per cent for their whole series. In Edinburgh, Lawrie and colleagues[6] reported a death rate of 23 per cent in 78 patients with supraventricular arrhythmias compared with a total of 17.5 per cent in their series of 400 patients. More specifically, the mortality rate in patients with atrial fibrillation in our series and in that of Stock was slightly higher than the total figure. In contrast, a mortality rate of 23 per cent in 17 patients with atrial tachycardia and atrial flutter in our series compares with a rate of 61 per cent in 18 patients with these arrhythmias described by Stock. The comparable figure in the Edinburgh series was 36 per cent in 30 patients.

Rigid conclusions are not warranted from such small numbers but in our series we considered that early D.C. shock with low energy discharges was particularly beneficial in patients with persistent atrial tachycardia or flutter. In contrast, digitalization remains the treatment of choice in patients with sustained atrial fibrillation.

D. E. Jewitt, M.B., B.Sc.(Lond.), M.R.C.P.
R. Balcon, M.B.(Lond.), M.R.C.P.
E. B. Raftery, M.B., B.Sc.(Lond.), M.R.C.P.
S. Oram, M.D.(Lond.), F.R.C.P.
Cardiac Department, King's College Hospital
London, S.E. 5, England

*Present address: Department of Medicine, Hammersmith Hospital, London, W.12, England.
**Present address: National Heart Hospital, London, W.1, England.

REFERENCES

1. Master, A. M., Dack, S., and Jaffe, L.: Disturbances of rate and rhythm in acute coronary artery thrombosis, Ann. Int. Med. 11:735, 1937.
2. Imperial, E. S., Carballo, R., and Zimmerman, H. A.: Disturbances of rate, rhythm, and conduction in acute myocardial infarction, Circulation 24:761, 1961.
3. Pick, A.: *In* Likoff, W., and Moyer, J. H., editors: Coronary heart disease, New York, 1963, Grune & Stratton, Inc., p. 129.
4. Julian, D. G., Valentine, P. A., and Miller, G. G.: Disturbances of rate, rhythm and conduction in acute myocardial infarction, Am. J. Med. 37:915, 1964.
5. Meltzer, L. E., and Kitchell, J. B.: Incidence of arrhythmias associated with acute myocardial infarction, Progr. Cardiovas. Dis. 9:50, 1966.
6. Lawrie, D. M., Greenwood, T. W., Goddard, M., Harvey, A. C., Donald, K. W., Julian, D. G., and Oliver, M. F.: A coronary care unit in the routine management of acute myocardial infarction, Lancet II:109, 1967.
7. Stock, E., Goble, A., and Sloman, G.: Assessment of arrhythmias in myocardial infarction, Brit. M. J. II:719, 1967.
8. Balcon, R., Jewitt, D. E., Davies, J. P. H., and Oram, S.: A controlled trial of propranolol in acute myocardial infarction, Lancet II:917, 1966.
9. Fluck, D. C., Olsen, E., Pentecost, B. L., Thomas, M., Fillmore, S. J., Shillingford, J. P., and Mounsey, J. P. D.: Natural history and clinical significance of arrhythmias after acute cardiac infarction, Brit. Heart J. 29:170, 1967.
10. Corday, E., Gold, H., De Vera, L. B., Williams, J., and Fields, J.: Effect of the cardiac arrhythmias on the coronary circulation, Ann. Int. Med. 50:535, 1959.
11. Vanfdar, J. P., and Levine, S. A.: Rarity of atrial tachycardia in acute myocardial infarction and thyrotoxicosis, Arch. Int. Med. 118:41, 1966.
12. Jewitt, D. E., Kishon, Y., and Shillingford, J. P.: The value of the right atrial ECG in the management of arrhythmias after acute myocardial infarction, Brit. Heart J. 30:97, 1968.
13. Lown, B., Fakhro, A. M., Hood, W. B., and Thorn, G. W.: The coronary care unit, J.A.M.A. 199:156, 1967.
14. Kleiger, R., and Lown, B.: Cardioversion and digitalis. II. Clinical studies, Circulation 33:878, 1966.
15. Jewitt, D. E., Balcon, R., and Oram, S.: Influence of propranolol on the mortality and complications of acute myocardial infarction, Brit. Heart J. 29:628, 1967.

Book reviews

RADIOLOGY OF THE HEART AND GREAT VESSELS. By Robert N Cooley M D and Melvyn H Schreiber M D second edition Baltimore, 1967 The William & Wilkins Company 4 566 pages Price $19.50

This monograph describes, in fairly great detail the method used in roentgenologic study of the heart and great vessels The illustrations selected are very good, and well labelled and supported by clear legends. The authors discuss technique and acquired and congenital heart disease from a clinical and anatomic as well as radiologic points of view Although most of the text is devoted to discussions of problems concerned with the heart and great vessels of the thorax, the abdominal vessels and aortograms and arteriograms are also presented Techniques and interpretations of findings are presented The bibliography and index are good This is a very useful book which is highly recommended among the many others already available on the subject

A SECOND PORTFOLIO OF CHEST RADIOGRAPHS. For Undergraduate and Postgraduate Students. By B T LeRoux, Ch M F.R C.S.E and T C. Dodds, F I M L.T Baltimore, 1968 The Williams & Wilkins Company 414 pages. Price $11 00

This is a very good book of chest radiographs. It consists of over 300 chest films with detailed descriptive legend illustrating the common diseases of the heart and lungs. The reproductions are very clear There is relatively little text included in the monograph and this is fine. The reader is really provided with a private course in interpretation of chest radiographs This is a very good book for students, interns, residents, and physicians who manage chest diseases.

CORONARY CIRCULATION IN THE NORMAL AND THE PATHOLOGIC HEART By Giorgio Baroldi, M D and Giuseppe Scomazzoni, M D Office of the Surgeon General, Department of the Army Washington, D C., 1967 304 pages. Price $4.50.

This monograph is based on the results of injections of coronary vessels of over 500 hearts with plastic material. The investigations were conducted at the Institute of Morbid Anatomy at the University of Milan, Milan, Italy and at the Armed Forces Institute of Pathology Washington D C. Normal as well as diseased hearts were studied. The presentation is brief and clear. The text is supported by many tables and excellent photographs of the injected vessels. These studies, as well as those reported by others, indicate the importance of such investigations of one of the most common diseases of man. This monograph is extremely good and summarizes much detailed work. The photographs also indicate the extent to which coronary angiography at present must improve to display adequately the coronary vessels in living patients. The bibliography contains over a thousand references and includes the important publications. This is a very good book on an extremely timely subject.

HEART DISEASE IN INFANTS, CHILDREN AND ADOLESCENTS. Edited by Arthur J Moss, M.D., and Forrest H Adams, M.D Baltimore, 1968, The Williams & Wilkins Co 1,140 pages. Price $[illegible]

This book edited by Doctor Moss and Doctor Adams with about 75 contributors in the field of pediatric cardiology and surgery is a somewhat encyclopedic presentation of cardiac diseases of infants and children. It is presented in a fashion similar to Cecil's well known Textbook of Medicine. The book includes embryology fetal circulation, genetics, history and physical examination, roentgenology electrocardiography vectorcardiography the congenital defects, infectious diseases, metabolic diseases special problems, and surgery as related to cardiac disease. As could be expected, the many aspects of cardiology offer a great deal of difficulty in presenting each problem in detail and still maintain a volume of a little over 1 100 pages Nevertheless, each aspect is handled very well and from a practical clinical point of view The illustrations are good, the printing excellent, and the bibliography though highly selected, is good and the index and appendix of standards of measurements and drugs with dosages are useful. This book is well done. It should be extremely valuable to all cardiologists, pediatricians, and internists. The price is high but much is provided in one volume. This should become a standard textbook and reference book on pediatric cardiology

American Heart Journal

March 1969 Volume 77 Number 3

Editorial

Coxsackie viruses and the heart

A. R. Grist, B.Sc., M.B., F.R.C.P.E., F.C.Path.
Eleanor J. Bell, B.Sc., Ph.D.
Glasgow, Scotland

Of all the viruses which may infect the heart, those incriminated most frequently belong to the picornavirus group. Encephalomyocarditis viruses and the agents of Teschen disease and foot and mouth disease can cause acute myocarditis in animals; in man, enteroviruses, notably poliovirus and particularly Coxsackie viruses, can cause heart disease.

In man, as in mouse, the newborn are susceptible to severe systemic infection by Coxsackie viruses. In conditions of moderate or poor hygiene, particularly in city or rural slums or in crowded underdeveloped countries where enteroviruses may be hyperendemic, most adults will be immune from infection in earlier life, and most newborn infants will be passively protected by maternal transmitted antibody. Under these conditions, primary infections with Coxsackie virus and other enteroviruses are acquired relatively harmlessly during the first few months of declining passive immunity or in the next few years of early childhood when the consequences are likely to be trivial in most cases, though some will manifest such complications as meningitis or acute myocarditis. Under the conditions of improved hygiene and slowed circulation of enteric flora, bacterial and viral alike, which characterize the more developed countries, it is to be expected that many persons will reach older and even adult years without having been infected and that this accumulation of susceptible persons will allow the appearance of periodic epidemics when temporary circumstances favor spread of an enterovirus.

This epidemiological shift consequent on improved hygiene and living conditions is illustrated by the well-known history of poliomyelitis which changed from a relatively minor endemic "infantile paralysis" problem into a periodic epidemic threat first in Northern Europe and North America and more recently in urban centers of many of the more slowly developing countries. Emergent activity of other enteroviruses (i.e., Coxsackie and ECHO viruses) is similarly evidenced by the familiar outbreaks of aseptic meningitis, "summer grippe," and Bornholm disease (the last not infrequently complicated by

From the University of Glasgow Department of Infectious Diseases and the Regional Virus Laboratory, Ruchill Hospital, Glasgow N. W., Scotland.

myopericarditis). Since nonimmune mothers and their newborn infants are vulnerable to these viruses, it is understandable that severe cases of neonatal infection by Coxsackie B viruses, sporadic or in nursery outbreaks, with myocarditis as a common feature and a usually high mortality rate, have been recognized in many areas since they were first reported in 1955.[29] Sometimes the infection is acquired from the mother, perhaps transplacentally.[7,18,19,20] Coxsackie myocarditis has been described in older children[31-33] and involvement of adults has been recognized increasingly during the decade since the first reports of Coxsackie pericarditis.[34-36] Coxsackie heart disease in adults was discussed in a recent editorial in this JOURNAL[37] and the probability that it is a common and important condition emerges from the reports of 10 adult cases by Smith[38] and of 22 cases by Sainani and associates[39] who listed reports of 38 other cases of Coxsackie B myo-pericarditis over the age of 12 years. Of our own 22 cases, 14 were in the second to seventh decades of life[40] as were also 16 of the 18 cases reported recently from Finland.[22] Both Smith and Sainani and co-workers discussed the possibility of Coxsackie B viruses causing endocardial as well as myocardial disease and perhaps chronic disease or permanent damage, and both had encountered cases with recurrent or persistent illness. Burch and colleagues[36-42] have reported experimental studies which together with their detection of Coxsackie B antigens in human cardiac myocytes and in fibrocytes of heart valves,[1, 40] suggest a possible mechanism for such disease processes.

The true incidence of Coxsackie carditis is difficult to determine because most reports concern "positive" cases and do not specify the background population of virologically negative cases with similar diseases or of infections by the same viruses without cardiac illnesses. However some impression can be gained from reports of the 1965 outbreak of Coxsackie B5 virus infection in Europe. Thus Coxsackie B5 virus was isolated from 12 of the 18 cardiac cases reported from Finland[22] and 4 other cases had serological evidence of this infection; the 18 cases comprised [illegible] per cent of the epidemic illnesses sufficiently severe to require admission to the King's hospital. Altogether during this outbreak 244 virus strains were isolated from [illegible] persons, 27 (12 per cent) of whom had cardiac illnesses; the population of the district numbered 270 000.[44] In Berlin 5 per cent of 900 people with Coxsackie B5 infections had cardiac disease.[45] In the Glasgow area of Scotland, cardiac syndromes comprised 2 (5 per cent) of [illegible] infections diagnosed by isolation of Coxsackie B5 virus, and 5 additional cardiac illnesses showed serological evidence of this infection; these 7 cardiac cases plus one of Bornholm disease made up 15 per cent of 53 cases of acute cardiac or pleurodynia-like illness investigated by us in 1965.[49] These figures underestimate the contribution of Coxsackie viruses to cardiac disease because of the limited proportion of cardiac cases investigated virologically and because of the practical difficulties of obtaining specimens sufficiently early in the course of infection to provide a good chance of isolating the virus and of detecting a significant rise in antibody titer.

In studies of sporadic cases of cardiac disease outside Coxsackie epidemic periods Johnson and associates[19] found evidence of Coxsackie B virus infection in each [illegible] of 34 patients. In Glasgow serological investigations of 24 sporadic cases in 19[illegible] through 1963 gave evidence of infection in 2 (based on rising antibody titers) plus 4 more with titers of 128 or more suggesting recent infection.[18] During the next [illegible] years 73 cases of cardiac disease and chest pain were investigated;[18] 40 of the patients had cardiac illnesses and of these 12 showed evidence of infection (5 with rising and [illegible] with falling antibody titers, 2 with titers over 512, and 2 with virus isolation alone). Of 57 cardiac illnesses of suspected viral origin investigated by Sainani and associates,[2] infection was found in 11 with raised antibody titers. Thus, evidence of Coxsackie B virus infection has been detected in from 3 to 39 per cent of such cases, many of them adults.

Most reports concern Coxsackie B virus infection, partly because this group of

ruses probably does cause most of the ouble, but also no doubt because most the group B viruses can be isolated adily in routine tissue cultures while e limited number (6) of antigenic types thin this group makes it feasible to tempt serological diagnosis in suitable cases. Much less is known about group A Coxsackie virus infections, partly because they probably contribute less to the problem of cardiac disease but also perhaps because most of them cannot be isolated in routine tissue cultures and must be detected by the inconvenient method of

ble 1 *Coxsackie group A virus infections in cardiac diseases*

Case No.	Ref	*Virology* Type	*Source of isolation*	*Serology**	*Age*	*Sex*	*Clinical diagnosis and summary*	*Heart† enlarged (x-ray)*	*ECG† abnormal*
1	36	A1	Feces	RT	74	M	Myopericarditis, fever and pain 1 week, recovered	+	+
2	40	A1	Feces	—	<1	F	Myocarditis, hyperpyrexia, convulsion, tachycardia, recovered slowly (months)	—	—
3	51	A4	Feces	—	6	M	Myocarditis, acute congestive failure, fever, recovered slowly (4½ months)	+	+
4	51	?A4	—	—	<1	M	Myocarditis, rapidly fatal, postmortem myocarditis	+	—
5	19	A4	Feces	—	1	F	Sudden death, postmortem myocarditis	—	—
6	19	A4	Feces, heart, and other organs	—	1	F	Sudden death, postmortem cardiac hypertrophy	—	—
7	32	A4	Feces	—	19	M	Myopericarditis, tachycardia and friction, recovered in 6 weeks	—	—
8	32	A4	Feces	—	1	F	Myocarditis, acute congestive failure recovered in 5 months	+	+
9	48	A4	Feces	100.233	29	F	Myopericarditis, acute congestive failure, fever and friction recovered gradually	+	+
10	22	A9	Feces	—	<1	M	Myocarditis improved		—
11	32	A9	Feces	RT	1	F	Myocarditis, acute congestive failure persisting, died after 4 months, postmortem myocarditis	+	+
12	52	A9	Nose, throat, and feces	512	<1	F	Myocarditis, acute congestive failure, died after 15 hours	—	+
13	33	A9	Feces	64 128	54	M	Myopericarditis, friction, recovered (17 days in hospital)	+	+
14	53	A16	Feces	—	<1	?	Myocarditis, died	—	—
15	54	A16	Feces, heart, and blood	—	<1	M	Myocarditis, acute tachycardia and cyanosis, died after 4 days, postmortem myocarditis	0	+
16	55	A23	Feces and throat	RT	<1	M	Myocarditis, paroxysmal atrial tachycardia	—	—
17	56	A23	Heart	8	34	M	Myocarditis, acute fever, block, fibrillation, died after 7 days, postmortem myocarditis	—	+

*RT = significantly rising antibody titer to homologous virus, figures = titers of antibody neutralizing homologous virus.
†+ = abnormality present; 0 = normal findings; — = not done or not recorded.

inoculating newborn mice. The formidable number (24) of antigenic types in this group makes routine serological diagnosis impracticable and in many cases even confirmatory serological tests for an already known or suspected type require inoculation of mice. Despite these difficulties, group A Coxsackie viruses have been isolated from a number of cases of cardiac disease. Table I lists 17 cases including one (Patient 4) in which no virological tests were done but the circumstances suggested infection of this patient by the same virus that infected his brother (Patient 3). Also included is one case of sudden death in infancy (Patient 6) with an abnormal heart but no proved myocarditis. Virus was isolated from the hearts of 3 patients (6, 15 and 17). Rising homologous antibody titers linking the infection with the disease in time were found in Patients 1, 11 and 16 (we have accepted as significant the neutralization index rise from 2.6 to 4 log units in Patient 1). Additional serological findings are as follows:

Patient 2. Neutralizing antibodies not found to Coxsackie B1, 2, 4, 5, 6; titers to Coxsackie B3 = 256:256.
Patient 9. Neutralizing antibodies not found to Coxsackie B1; titers to Coxsackie B5 = 128:64.
Patient 13. Neutralizing antibody titers to Coxsackie B3 = >256:>256; to Coxsackie B5 = 256:256.

It must be admitted that in the absence of controls and full serological data it is impossible to be sure how many of the listed infections were etiologically significant and whether some may have been coincidental and irrelevant to cardiac disease. Nevertheless, the evidence that the virus infections were causal, not casual, is virtually conclusive in Patients 1, 6, 11, 15, 16 and 17, and the series as a whole is very similar to the more familiar Coxsackie B cases which have been reported over the years since 1955.

Enteroviruses are so widespread and infections with them so common that it is fortunate that ECHO viruses do not appear to be significant causes of cardiac disease. Among enteroviruses the ability to infect the heart may be correlated with ability to cause myositis in immature rodents (characteristic of Coxsackie but not ECHO viruses). ECHO 9 virus was reclassified as Coxsackie A23 virus when its pathogenicity for suckling mice was discovered[47] and 2 cases of this infection are tabulated (Patients 16 and 17). Pleurodynia has also been reported in this infection.[48] Since ECHO 6 virus has also been reported to be adaptable to suckling mice producing Coxsackie B-like changes, it is interesting that we have found ECHO 6 infections in 2 cases of Bornholm disease and one of chest pain and pericarditis with thoracic zoster.[22, 48]

If, despite practical difficulties of virological diagnosis, group B Coxsackie virus infections can be demonstrated in up to 39 per cent of cases of otherwise unexplained acute myocarditis and pericarditis and if an additional proportion of these cases is due to group A Coxsackie and occasionally to ECHO virus infections, it appears that the majority of such can be etiologically explained. Now that paralytic poliomyelitis can be prevented by immunization, perhaps the most serious future manifestation of enterovirus infection will be cardiac damage by Coxsackie viruses resulting in acute myo/pericarditis and sequelae thereof, and even developmental abnormalities as a consequence of fetal infection.[49]

REFERENCES

1. Montgomery, J., Gear, J. H. S., Prinsloo, F. R., Kahn, M., and Kirsch, Z. G.: Myocarditis of the newborn. An outbreak in a maternity home in Southern Rhodesia associated with Coxsackie group-B virus infection, South African M. J. 29:608, 1955.
2. Javett, S. N., Heymann, S., Mundel, B., Pepler, W. J., Lurie, H. I., Gear, J. H. S., Measroch, V., and Kirsch, Z. G.: Myocarditis in the newborn infant. A study of an outbreak associated with Coxsackie group B virus infection in a maternity home in Johannesburg, J. Pediat. 48:1, 1956.
3. Gear, J. H. S., Measroch, V., and Prinsloo, F. R.: The medical and public health importance of the Coxsackie viruses, South African M. J. 30:806, 1956.
4. DeJong, F.: Myocarditis bij zuigelingen veroorzaakt door het Coxsackie virus groep B, Nederl. Tijdschr. v. Geneesk. 99:2676, 1955.
5. Van Creveld, S., and De Jager, H.: Myocarditis in newborns caused by Coxsackie virus, Ann. paediat. 187:100, 1956.
6. Verlinde, J. D., Van Tongeren, H. A. E., and Kret, A.: Myocarditis in newborns due to group B Coxsackie virus, Ann. paediat. 187:113, 1956.

7. Kibrick, S. and Benirschke, K. Acute aseptic myocarditis and meningoencephalitis in the newborn child infected with Coxsackie virus group B, type 3, New England J. Med. 255:883, 1956.
8. Sabin, A. Comment, *in* Year book of pediatrics, Chicago, 1958, Year Book Medical Publishers, Inc., 1957-1958 series, p. 269.
9. Kibrick, S., and Benirschke, K. Severe generalized disease (encephalohepatomyocarditis) occurring in the newborn period and due to infection with Coxsackie virus, group B, Pediatrics 22:857, 1958.
10. Sussman, P. V., and Vogelpoel, L. Coxsackie myocarditis of the newborn, M. Proc. 4:372, 1958.
11. Simenhoff, M. L., and Uys, C. J. Coxsackie virus myocarditis of the newborn, a pathological survey of four cases, M. Proc. 4:389, 1958.
12. Naudé, W. D. T., Selzer, G., and Kipps, A. Coxsackie virus myocarditis of the newborn, M. Proc. 4:397, 1958.
13. Kipps, A., Naudé, W. D. T., Don, P., and Cooper, E. D. Coxsackie virus myocarditis of the newborn, M. Proc. 4:401, 1958.
14. Delaney, T. B., and Fukunaga, F. H. Myocarditis in a newborn infant with encephalomeningitis due to Coxsackie virus group B, type 5, New England J. Med. 259:234, 1958.
15. Rapmund, G., Gauld, J. R., Rogers, N. G., and Holmes, G. E. Neonatal myocarditis and meningoencephalitis due to Coxsackie virus group B, type 4, New England J. Med. 260:819, 1959.
16. Vasek, J., Lukes, J., Potuznik, V., Polodnikova, I., and Vikm, V. Myocarditis and encephalitis in newborn infants caused by Coxsackie B virus, J. Hyg. Epidem. Microbiol. Imm. 3:283, 1959.
17. Moossy, J., and Geer, J. C. Encephalomyelitis, myocarditis, and adrenal cortical necrosis in Coxsackie B3 virus infection, Arch. Path. 70:614, 1960.
18. McLean, D. M., Donohue, W. L., Snelling, C. E., and Wyllie, J. C. Coxsackie B5 virus as a cause of neonatal encephalitis and myocarditis, Canad. M. A. J. 85:1046, 1961.
19. Gold, E., Carver, D. H., Heineberg, H., Adelson, L., and Robbins, F. C. Viral infection, a possible cause of sudden, unexpected death in infants, New England J. Med. 264:53, 1961.
20. Jennings, R. C. Coxsackie group B fatal neonatal myocarditis associated with cardiomegaly, J. Clin. Path. 19:325, 1966.
21. Varraia, E., and Castelli, L. Su di un caso di miocardite da Coxsackie B5, Rc. Ist. sup. Sanità 20:831, 1957.
22. Hosier, D. M., and Newton, W. A. Serious Coxsackie infection in infants and children, Am. J. Dis. Child. 96:251, 1958.
23. McLean, D. M., Croft, C. C., Prince, J. T., and Heckmann, F. E. Coxsackie and ECHO virus infections in Ohio during 1956, Ohio State M. J. 53:907, 1956.
24. McLean, D. M., Walker, S. J., and Bain, H. W. Coxsackie B5 virus in association with pericarditis and pleurodynia, Canad. M. A. J. 79:789, 1958.
25. Kagan, H., and Bernkopf, H. Pericarditis caused by Coxsackie virus B, Ann. paediat. 189:44, 1957.
26. Walker, S. J., McNaughton, G. A., and McLean, D. M. Coxsackie B5 virus infections in children, Toronto, 1958, Canad. J. Public Health 50:161, 1959.
27. Woodward, T. E., McCrumb, F. R., Carey, T. N., and Togo, Y. Viral and rickettsial causes of cardiac disease, including the Coxsackie virus etiology of pericarditis and myocarditis, Ann. Int. Med. 53:1130, 1960.
28. Connolly, J. H. Myocarditis during Coxsackie B5 infection, Brit. M. J. 1:877, 1961.
29. Rentsch, M. Les infections à virus Coxsackie de l'enfant, Rev. méd. Suisse romande 81:133, 1961.
30. Babb, J. M., Stoneman, M. E. R., and Stern, H. Myocarditis and croup caused by Coxsackie virus type B5, Arch. Dis. Child. 36:551, 1961.
31. Strõm, J. Coxsackie B5 infection causing serous meningitis with exanthema and benign pericarditis with myocarditis in two siblings, Acta paediat. (Suppl.) 135:197, 1962.
32. Grist, N. R. Viral cardiomyopathy, Symposium, Disorders of the Heart and Circulation, Royal College of Physicians of Edinburgh Publication No. 31, Constable, Edinburgh, 1966.
33. Helin, M., Savola, J., and Lapinleimu, K. Cardiac manifestations during a Coxsackie B5 epidemic, Brit. M. J. 3:97, 1968.
34. Fletcher, E., and Brennan, C. F. Cardiac complications of Coxsackie-virus infection, Lancet 1:913, 1957.
35. Fletcher, E., and Brennan, C. F. Cardiac complications of Coxsackie-virus infection, Lancet 2:585, 1958.
36. Movitt, E. R., Lennette, E. H., Mangum, J. F., Berk, M., and Bowman, M. S. Acute benign pericarditis. Report of two cases associated with group A and group B Coxsackie viruses, New England J. Med. 258:1082, 1958.
37. Smith, W. G. Coxsackie heart disease in adults, Am. Heart J. 73:439, 1967.
38. Smith, W. G. Adult heart disease due to the Coxsackie virus group B, Brit. Heart J. 28:204, 1966.
39. Sainani, G. S., Krompotic, E., and Slodki, S. J. Adult heart disease due to the Coxsackie virus B infection, Medicine 47:133, 1968.
40. Grist, N. R., and Bell, E. J. Coxsackie virus heart disease, Brit. M. J. 3:556, 1968.
41. Burch, G. E., DePasquale, N. P., Sun, S. C., Mogabgab, W. J., and Hale, A. R. Endocarditis in mice infected with Coxsackie virus B, Science 151:447, 1966.
42. Burch, G. E., DePasquale, N. P., Sun, S. C., Hale, A. R., and Mogabgab, W. J. Experimental Coxsackie virus endocarditis, J. A. M. A. 196:349, 1966.
43. DePasquale, N. P., Burch, G. E., Sun, S. C., Hale, A. R., and Mogabgab, W. J. Experi-

mental C xsackie vir B4 v lvul tis in cyno- molgus monkey Am Heart J 71:678, 1966.
44 Burch G F Sun S C Chu K C Sohal R S and Colcolough H I I terstitial and Coxsackievirus B myocard tis in inf nts nd hildren J A M A 203 1 1968
45 Burch, G E Sun S C Colcolough H L Sohal R S and DePasquale N P Cox sackie B viral myocard tis nd valvul tis iden- t fied n outine utopsy specimens by im- munofluorescent tech iques Am Heart J 4 13 1967
46 Lapinleimu K Hel M nd Su ola, J : Cardiac ma ifestations during Coxsackie B5 epidemic comm nication read to Third Scottish-Scand navian Conference on Infec tious Diseases, T rku June 8 1968
47 Report to Director of Public Health Laboratory Service f om arious laboratories in the United Kingdom Coxsackie B5 irus infections during 1965 Brit M J 4:575 1967
48 Bell F J nd C ist N R Coxsackie irus infections patient w th acut cardiac dis- ease and hest pai Scot M J 13:47 1968
49 Johnson, R T Portnoy B Rogers, N G nd Buescher F I Acute benign pericard tis, Arch I t Med 108:823, 1961
50 Middleton P J and G ist N R A serological estig t on of Coxsa kie virus g oup B infec tion in patient w th cardiac disease and chest pa Scot M J 10 108 1965
51 De Goes, P De Paola, D Bruno-Lobo, M and Dias, L D Miocard te por virus Cox sackie d gr po A A Microbiol 7 13 1959
52. Chrstodoulopoulou G., and Rimell, ? Myocarditis due t Coxsackie group A ty virus—clinical and experimental stud, ? ges. Virusforsch. 23 71 1968.
53 Magoffi R L., Jackson, E. W and ? E. H Vesicular stomatitis and exanthem yndrome associated with Coxsackie ? type A16, J A. M A. 175:441, 1961.
54 Wright, H. T Landing, B. B Lennette, E H and McAllister R. M : Fatal infection an infant associated with Coxsackie ? group A type 16, New England J Med 2? 1041 1963.
55 Cherry J D Jah C. L., and Meyer, T C P roxysmal atrial tachycardia associated ? Echo 9 virus nfection, Am Heart J 73: 1967
56 Monif G R. G Lee, C. W and Hsiung, G D Isolated myocarditis with recovery ? Echo type 9 virus from the myocardium ? England J Med. 277 1353, 1967
57 Sickles, G. M Mutterer M and Plager, H New types of Coxsackie virus, Group ? cytopathogenicity n tissue culture, Proc Soc Exper Biol. & Med 102:742, 1959.
58 Sanford, J P and Sulkin, S E The clinical spectrum of Echo-virus infection, New England J Med 261 1113 1959
59 Vasilenko, S. and Atanov S. Experimental infections of mice with Echo 6 virus, ? virol. 9:541 1965
60 Brow G. C., and Evans, T N Serologic evidence of Coxsackie virus etiology of con ge ital heart disease, J A M A 199:183, 1967

Clinical communications

Dissecting aneurysm complicating Marfan's syndrome (arachnodactyly) in a mother and son

Claude M. Grondin, M.D.
Charles L. Steinberg, M.D.
Jesse E. Edwards, M.D.
Minneapolis, Minn.

A hereditary tendency in Marfan's syndrome (arachnodactyly) is recognized but relatively few cases have been documented with necropsy. This phenomenon was represented by the occurrence of this syndrome in a mother and son which came to our attention. In each, dissecting aneurysm of the aorta was demonstrated pathologically as a major complication. In the son, deformities of the atrioventricular valves were of additional interest. As far as we are aware, there is only one other report in which close relatives with Marfan's syndrome each suffered from dissecting aneurysm of the aorta as supported by necropsy findings.

This phenomenon was described by Whittaker and Sheehan in 1954. A father suffered from dissecting aneurysm at the age of 46 years and his son experienced the same condition when he was 27 years old.

The purpose of this report is to place on record a second family with Marfan's syndrome in which dissecting aneurysm occurred in close relatives.

Case reports

Case 1

CLINICAL FEATURES. A 30-year-old housewife in the twenty-second week of her third pregnancy was admitted to The Charles T. Miller Hospital in October 1955 with a 48 hour history of substernal pain radiating to the jaws and to the interscapular region.

Physical examination revealed dolichostenomelia, arachnodactyly, scoliosis of the thoracic spine, and pectus carinatum. There were no ocular symptoms or abnormal signs. A loud systolic murmur was heard loudest over the left sternal border at the level of the third intercostal space and it radiated to the neck. No diastolic murmur could be heard. The pulse rate was 60 per minute and regular. The right arm and hand were cool and clammy.

The blood pressure averaged 140 mm. Hg systolic and 55 mm. Hg diastolic in the left arm. In the right arm, the pressure at first unobtainable, leveled to 70 mm. Hg and this discrepancy persisted throughout the remainder of her life.

The patient's condition stabilized during the next 10 days. Three months later a cesarean section and tubal ligation were performed. Congestive cardiac failure developed 6 months later and the patient was rehospitalized. At that time, a Grade III/IV diastolic murmur over the left sternal border and a muffled systolic murmur were heard, the latter radiating to the left axilla.

While in a state of congestive cardiac failure

From the Department of Pathology, The Charles T. Miller and The Children's Hospitals, St. Paul, Minn., and the Departments of Surgery and Pathology, University of Minnesota, Minneapolis, Minn.
This study was supported by Public Health Service Research Grant 5 RO1 HE05694 and Research Training Grant 2 T1 HE05570 from the National Heart Institute.
Received for publication Dec. 21, 1967.

Details of this case were reported by Hawley and associates.

the patient died suddenly at home in December 1956 nearly 14 months after the first admission.

Roentgenograms taken during both hospital admissions had confirmed the clinical diagnosis of dilatation of the ascending aorta and progressive cardiac enlargement. The electrocardiographic tracings showed left axis deviation and left ventricular hypertrophy.



Fig. *1* Case 1 Gross specimen showing large left ventricular cavity and dissecting aneurysms of the ascending aorta. The intimal tear (*A A*) in the ascending aorta leads to the first dissecting channel (*1*). Near the left subclavian artery (*LS*) a second tear (*B B*) leads to a second dissecting channel (*2*). Both re-enter the original aortic lumen (*O*) at a point (*C C*) above the renal arteries.

FAMILY HISTORY The patient is the youngest member of a family of 4. Her sister 41 years of age has been in a mental hospital since the age of 8 with a diagnosis of Mongolism. According to the institutional records, she has no physical deformities, cardiac murmur or ocular malformations. Two brothers, now 50 and 42 years of age, are living and well with no physical deformities or cardiac murmurs. The father died at the age of 65 of unknown cause and the mother is alive and well at the age of 80. Neither parent exhibited physical deformities, ocular malformations, or cardiac disease.

Of the patient's three children, each of whom are boys, only the oldest now 16 years old, is normal. The youngest, now 11 years old, exhibits typical features of Marfan's syndrome and a pectus excavatum type of deformity of the sternum. In the middle sibling since the age of five years the ascending aorta has been noticeably enlarged and aortic insufficiency is currently present. The second sibling represents Case 2 of this report and will be described in a forthcoming section.

PATHOLOGIC FEATURES. The major pathologic findings were limited to the cardiovascular system. Marked enlargement of the left ventricular cavity was present. The left atrium and right ventricle were moderately enlarged. In the ascending aorta 3 cm above the posterior and right aortic cusps was a 6 cm. transverse tear which led to a large false passage within the aortic wall. The dissection proceeded distally to encompass the brachiocephalic vessels. It then descended on the left side posteriorly in the descending thoracic aorta and re-entered the original lumen of the aorta just above the level of the renal arteries. A small vertical tear was noted in the posterior wall of the false passage near the left subclavian artery and from this tear a second dissecting aneurysm proceeded downward to the level of the renal arteries, where it re-entered the first described and larger false channel (Figs. 1 and 2). The walls of both dissecting aneurysms were

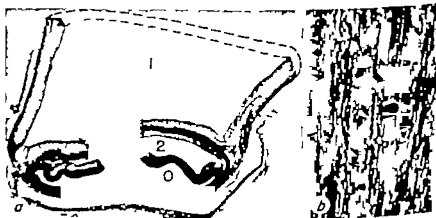


Fig. *2* Case 1 Photomicrograph of cross-section of thoracic aorta showing the 3 channels. *0* Natural lumen of aorta. *1* major false passage. *2* false passage within wall of first false passage. ELVG X3. *b*, Photomicrograph of media of ascending aorta showing multiple cystic spaces and loss of elastic laminae. Elastic van Gieson tal ×100.

-eared old and partly endothelialized. The larger -ble channel exhibited retrograde dissection near he right aortic cusp but the ostium of the right oronary artery was not narrowed. Most of the ntercostal arteries had been severed from the main ortic channel but none of the abdominal vessels vas involved.

The aortic cusps were elongated and tended to rolapse. The pulmonary trunk, pulmonary valve, and tricuspid valve were normal. The leaflets of the itral valve were thick, rubbery and somewhat edundant. The left entricle was huge. The left entricular wall measured 1 7 cm. i thickness. he papillary muscles appeared flattened, thin, and ty. The chordae tendineae ere thin and free of dhesions. The left trium was large and thick valled. No jet lesions were seen but that mitral sufficiency had been present during life could not e excluded.

Histologic examination of representative sections rom the ascending nd descending portions of the orta showed multiple foci of classical cystic medial ecrosis (Fig 2 b). Such foci were represented by ools of basophilic material replacing elements of he aortic media.

Case 2

CLINICAL FEATURES. The patient was the second on of the patient in Case 1. At 6 years of age he nderwent correction of severe pectus excavatum. He remained asymptomatic until the age of 10 years when he was admitted to hospital for pre-cordial pain and low grade fever. A clinical diag nosis of pericarditis was made and wa substanti-ted by the electrocardiographic findings. Recovery was uneventful. At the ge of 12 years in 1963 a second episode of precordial pain prompted more detailed cardiovascular investigation. The blood pressure on this second admission was 115 mm. Hg systolic and 80 mm. Hg diastolic in each arm. A loud, Grade III/IV late, systolic murmur hich as heard t the apex, radiated to the left axilla.

Physical examination revealed arachnodactyly high arched palate, and moderate thoracic scoliosis. The ophthalmologic examination failed to disclose any abnormality. The electrocardiogram revealed signs of left axis deviation, left entricular hypertrophy nd left atrial hypertrophy.

A retrograde aortogram (Fig 3) disclosed marked dilatation of the ascending orta beginning t the level of the aortic sl uses and tapering t the arch. The rest of the thoracic aorta was of normal caliber but was tortuous, so that bov the diaphragm pronounced kink of almost 90 degrees was present. The abdominal aorta and its major branches were also unusually long. The aortic valve wa competent. A left ventriculogram disclosed left ventricular enlargement and Grade II III/IV mitral insufficiency. A peculiar configuration of the mitral leaflets was apparent (Fig 3 b). When reviewed in the light of the necropsy findings, it became evident that this represented an unusual and probably pathognomonic picture. The mitral leaflets were divided int several large serrations which bulged into the left atrium.

The patient clinical condition was not judged



Fig 3 Case 2 Lateral iew of retrograde aortogram showing the dilated ascending aorta, the competent aortic alve, nd the unusually tortuous descending thoracic aorta. b Lateral view of left ventriculogram showing the severe mitral regurgitation and the large serrations (between arrow) in the leaflets of the mitral valve.

serious enough t w rra t mitral al la eplacement or resection of the dilated ascending aorta

One year later t the age of 13 years, the patient experienced sudden onset of severe pain in the back while lying i bed He rapidly becam dyspneic and died within few min tes

PATHOLOGIC FEATURES At necropsy 500 ml of blood were found in the pericardial cavity The ascending orta as dilated. Examination of the interior of the aorta revealed large right angle tea 4 cm above the posterior aortic sinus This led into a false channel within the medial layer of the orta (Fig 4) a picture classical for dissecting neurysm. The dissection had progressed in retrograde fashion to encircle and obstruct the proximal 2 cm of the right coronary artery Distally, the false channel continued t a level just distal to the origi of the left subcla ian artery where it entered the natural ortic lumen. I the adventitial layer of the ascending orta below the pericardial reflection there was a 2 cm vertical tear that served tract through which bleeding into the pericardium had occurred



Fig 4 Case 2 Gross specimen showing right ngled tear (bet een proximal arrow) in dilated ascend ng orta and re-entry (between distal arrows) of dissecting neurysm just below the left subclavian rtery

The aortic cusps were large and ... elongated The coronary ostia lay at ... level ... than usual

The left entricular ca ity as of normal ... The left entricle was hypertrophied, measuring 1 8 mm in the free all There ere no jet lesions ... the left entricula outflow tract. The right atrium and right entricle ere moderately dilated The pulmonary trunk and pulmonary valve ere ... The trio entricula valves showed unusual changes more marked the mitral than the tricuspid valve From bove each alve showed numerous protrusion tow rd the related trium (Fig 5) These were represented by upward protrusion of the ... lvular nits bet een the insertions of chordae (Fig 6). The ndividual chordae ere thin but did not seem u sually long Incompetence of the m tral alve observed clinically and angiocardiographically ppeared t ha e resulted from ... about of the individual protrusions of the leaflets

Sections of the ascending and descending aorta ... nd of the brachiocephalic arteries showed cystic medial necrosis. The leaflets of the atrioventricular al were markedly thickened. When stained for acid mucopolysaccharides, they showed ... accumulation of chondroitin sulfate as evidenced by the d sappearance of the blue stain ...



Fig 5 Case 2. M tral alve nd *b* tricuspid al each from bo e. I each, interchordal protrusions of the leaflets present toward the related trium

hyaluronidase was utilized prior to the colloidal ion solution.

Comment

A hereditary trait in a patient with arachnodactyly was first reported in 1902.[3] In a recent review McKusick stating that the disease is autosomal dominant estimated that de novo mutation is seen in only 5 per cent of the cases. Although arachnodactyly may be present at birth a period of latency is usually seen before outward manifestations become apparent. The penetrance and expressivity may vary The skeletal cardiac or ocular manifestations may *therefore be partial or complete* Ectopia of the lenses is present in 50 to 70 per cent of patients. Cardiovascular complications may be expected to occur in 30 to 60 per cent of the cases The skeletal deformities constitute the most frequent manifestations of the disease.

Aneurysmal dilatation of the ascending aorta with or without dissecting aneurysm is the cardiovascular lesion most frequently encountered It should be pointed out that the diagnosis of Marfan's syndrome in a tall patient presenting with aneurysm of the ascending aorta becomes doubtful if the family history is negative or when no skeletal deformities are present



Fig. 4 Case 2. A portion of opened mitral valve viewed from behind. I terchordal segments of leaflet tissue conspicuously bulge upward toward left atrium (*L.A.*). *L.V* Left ventricle

It is generally agreed[4] that atrial or ventricular septal defects which were given emphasis in the early reports as related to Marfan's syndrome are probably coincidental Moreover in most instances wherein atrial septal defect was claimed the process was a patent foramen ovale.

Lesions of the atrioventricular valves seem to occur more often than indicated in the literature There is evidence that the lesions affecting the aorta and the atrioventricular valves have histochemical similarities.[4] In the aortic media, mucopolysaccharides accumulate in pools between elastic laminae or in place of elastic laminae The relationship between this accumulation of mucoid material and loss of elastic tissue is still unclear

Erdheim[7] was of the opinion that the mucoid material which normally lays between elastic fibers gradually enlarges to effect loss both of elastic and muscular fibers As the latter disappear the small foci become confluent and form cystic spaces. Others[8] consider this mucoid material a product of disintegration of the elastic fibers. Hurley expressed the view that the loss of elastic and muscular fibers is similar to that which occurs with aging

Increase in acid mucopolysaccharides which has been found in the aortic media of patients with Marfan's syndrome has also been observed in the atrioventricular valves.

As in the aortic media, it is presumed that the connective tissue defect manifested histochemically by accumulation of acid mucopolysaccharides is responsible for elongation stretching and redundancy of leaflet tissue. The lesions of the atrioventricular valves, like those affecting the great vessels, tend to occur more commonly on the left side, a phenomenon believed to be largely dependent on hemodynamic stresses

Other factors such as sex pregnancy and hypertension may also be pertinent to the location and development of the cardiovascular lesions. While the aortic lesions are seen more often in men the mitral lesion tends to occur in young women.[4] A predilection for dissecting aneurysm during pregnancy has been observed by several authors.[11-13] In 70 cases of dissecting aneurysm occurring in women under the age of

years reviewed by Mandel and associates[14] 36 (51 per cent) occurred in association with pregnancy An analogy to the effects of the hormone relaxin on the connective tissue has been postulated[12] but experimental induction of dissecting aneurysm in animals injected with relaxin and rendered hypertensive has not been successful[4] There is little information available on histochemical changes of the aortic media during pregnancy In one reported series of 7 patients who died during pregnancy of causes other than dissecting aneurysm accumulation of mucoid material in the media of the ascending aorta was found in 6.[12]

Hirst and associates[13] observed among pregnant women that more than half with dissecting aneurysm were hypertensive and postulated that the histochemical changes which occur in the aorta during pregnancy favor the occurrence of dissecting aneurysm rather than precipitate it. Only a small proportion of the reported cases of dissecting aneurysm during pregnancy was associated with arachnodactyly This may represent the fact that the diagnosis of Marfan's syndrome was not entertained in many of the earlier reports.

Summary

Few reports of dissecting aneurysm of the ascending aorta among close relatives have appeared in the literature and in only one previous report was this described in association with Marfan's syndrome.

Reported are the cases of a mother and son each with Marfan's syndrome (arachnodactyly) and dissecting aneurysm of the aorta. In the mother dissecting aneurysm occurred when she was 30 years old and pregnant with her third offspring Death occurred at the age of 31 years after aortic insufficiency and congestive cardiac failure had developed.

The son was the second offspring [illegible] died of acute dissecting aneurysm when [illegible] was 13 years old In the son, [illegible] protrusions of the leaflets of the [illegible] and mitral valves were considered manifestations of Marfan's syndrome. Mitral [illegible] sufficiency had been identified clinical[illegible]

REFERENCES

1 Whittaker S. R. F and Sheehan, J D [illegible] secting aortic aneurysm in Marfan [illegible] Lancet [illegible] 791 1954.

2. Husebye K. O Wolff H. J and Fried[illegible] L. L. Aortic dissection in pregnancy [illegible] of Marfan's syndrome, Am. Heart J [illegible] 1958.

3 Achard M C. Arachnodactylie, Bull [illegible] Soc. méd. hôp. Paris 19:834 1902.

4 McKusick, V A Heritable disorders of [illegible] nective tissue ed. 2, St. Louis, 1960, The C. Mosby Company

5 Goyette, E. M and Palmer P E. [illegible] vascular lesions in arachnodactyly Circ[illegible] [illegible]373, 1953.

6. Grondin, C. M and Edwards, J. E [illegible] mitral valve in the Marfan syndrome [illegible] published data.

7 Erdheim, J Medionecrosis aortae idiopathica cystica, Virchows Arch. Path. Anat. 27[illegible] 1930.

8. Cellina, M Medionecrosis [illegible] Virchows Arch. Path. Anat. [illegible]

9 Rottino, A. Medial degeneration of aorta [illegible] seen in 12 cases of dissecting aneurysm, Arch Path. 28 1 1939

10. Hurley J V Marfan syndrome The [illegible] of the aortic defect, Australasian Ann Med [illegible] 8:45 1959

11 Schnitker M A and Bayer C A Dissecting aneurysm of aorta in young individuals [illegible] ticularly in association with pregnancy, [illegible] report of case, Ann. Int. Med. 20:486, [illegible]

12 Sheehan, H L. Pathology of obstetric [illegible] J Obst. & Gynaec. Brit. Emp. 46:218, [illegible]

13 Hirst, A. E., Johns, V J Jr and Kime, S [illegible] J Dissecting aneurysm of the aorta [illegible] of 505 cases, Medicine 37:217 1958

14 Mandel, W Evans E. W and Walford, R L Dissecting aortic aneurysm during pregnancy New England J Med 251 1059, 1954.

Restrictive cardiomyopathy as the presenting feature of reticulum cell sarcoma

Allen Kaplan M.D
*Jules Cohen M.D***
Rochester N. Y

The myocardium may become involved secondarily in patients with a variety of systemic disease processes and cardiomyopathy may develop in the absence of the common etiologic forms of heart disease. Infiltration of the myocardium secondary to systemic disease, represents one such type of cardiomyopathy and may be seen, for example with amyloidosis, sarcoidosis, hemochromatosis, and certain glycogen storage diseases.

Infiltration of the myocardium in the lymphoproliferative disorders with production of clinical heart disease is extremely uncommon although pathologic evidence of myocardial infiltration with tumor is much more often encountered. Goodwin and associates[1] described a case of Hodgkin's sarcoma with features of what they called restrictive cardiomyopathy the clinical and hemodynamic findings resembling those of constrictive pericarditis. At postmortem examination infiltration of the pericardium, myocardium and endocardium with tumor was found. The present paper reports the case of a patient with reticulum cell sarcoma who initially was thought to have an obscure restrictive cardiomyopathy later developed disseminated lymphoma, and improved significantly following mediastinal irradiation.

Case report

P tient D P 45-year-old Caucasian woman was admitted t Strong Memorial Hospital in October 1964, with six-month history of fatigue and increasing dyspnea. She had past history of poliomyelitis at age 1½ with residual right hemiparesis and grand mal seizures the latter had been treated with diphenylhydantoin and phenobarbital. She had no past history of angina, hypertension rheumatic fever heart murmur syphilis, diabetes, or lcoholism Her sister died t age 35 of an illness characterized by heart failure lymphadenopathy and hepatosplenomegaly Both biopsy and postmortem material were interpreted as showing only typical lymphoid hyperplasia

Physical examination in 1964 revealed a blood pressure of 100/80 respiratory rate of 20 per minute, and an irregular pulse t rate of 80. The neck veins were described as normal. Fine inspiratory râles were heard t both lung bases. The apical impulse of the heart was in the fifth interspace in the anterior axillary line A fourth heart sound as

From the Cardiopulmonary Unit, Department of Medicine and the Medical Clinics, University of Rochester Medical Center, Rochester N. Y

Supported in part by grants-in-aid (HE 0795 and 05964) from the National Heart Institute, United States Public Health Service, New York State Heart Assembly and Genesee Valley Heart Association.
Received for publication March 15 1968

*Formerly Assistant Resident Physician, Strong Memorial Hospital, Rochester N. Y. Present Clinical Associate National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.
**Assistant Professor of Medicine and Associate Physician, University of Rochester Medical Center Rochester N. Y

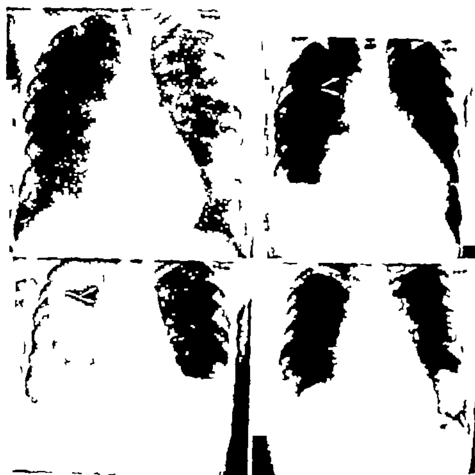
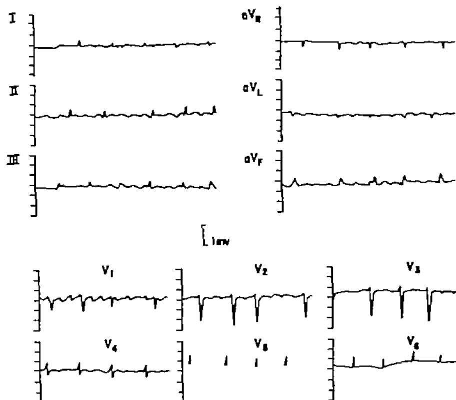


Fig 1 Serial posteroanterior chest oentgenograms Upper left panel, in tial film Nov 4 1964 Moderate cardiac enlargement is present with little evidence of pulmonary congestion. Oblique view demonstrated right ventricular left atrial and left en ricular enlargement. Upper right panel, M y 25 1965 Note the great cardiac enlargement, right pleural effusion nd suggestion (arrow) of right superior mediastinal mass. Lower left panel Ma 2 1966, 3 weeks after ompletion of therapy Note the left pleural effusion. The heart size is now normal, and had been so before radiation therapy was begun, as the result of treatment for cardiac failure. The right superior mediastinal mass is clearly evident (arrow). Lower right panel, June 6 1967 Resolution of the mass is pparent The changes in the lungs are probably related to the radiat on therapy Heart size normal

present t the cardiac pex. There were no murmurs The pulmonary valv losu sound seemed accentuated The liver was palpable 4 cm below the right costal margin The spleen was not palpable There was no edema A ight hemiparesis with diminished gag reflex on the right fasciculation the right arm, nd bilaterally positiv H ffman sign were present

Laboratory data The hematocrit was 41 per cent the whit blood cell count was 7,300 w th ormal differential. Results of a urinalysi wer negative and result of tests for blood urea nitrogen fasting blood glucose, serum electrolytes, calci m serum glutamic oxaloacetic transaminase alkaline phosphatase, protein electrophoresis, Bromsulphophthalein retention, and protei -bound iodine were all within normal limits. Intermediate strength purified protein derivativ was negative Chest roentgenograms n 4 projections, th barium swallow demonstrated an enlarged left trium prominent left entricle and encroachment on the retrosternal pac by th right ventricle (Fig 1). Atrial fibrillation with variable A V block nd low oltage on lectrocardiogram (Fig 2). A rectal biopsy ielded normal results.

The findings of cardiac catheterization are shown in Tables I nd II nd in Fig 3 The right atrial nd right ventricular pressures varied with respiration. Th e were no pressure gradients across any of the 4 valves. A rapid y descent was seen in the right trial tracing nd sharp a and v waves with rapid "x nd "y descents were present in the left trial tracing Both left and right ventricular pressure curves had dip-plateau configur



2. Initial electrocardiogram. Note the low voltage. The rhythm is atrial flutter with variable block. Nonspecific T-wave changes are present.

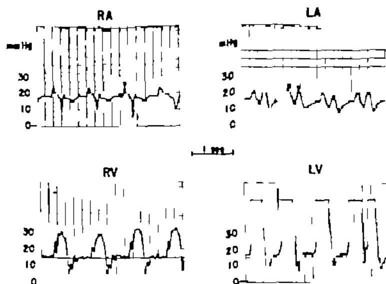


Fig. 3 Results of initial cardiac catheterization on Nov. 17, 1964. Note the high mean right atrial (RA) pressure, with rapid "y" descent (upper left), the high mean left atrial (LA) pressure with sharp and "v" waves and rapid "x" and "y" descents, the early diastolic pressure dip and high end-diastolic plateau in both the right and left ventricular pressure pulses (RV, LV). The findings are characteristic of restrictive process.

t n Th cardiac output was subnormal (1 7 L. per minut per square meter). Intra venous ouabai produced hange th rate of ri-e of left ventricula pressure (dp/dt) but th mean pulmonary artery nd left entricula end-diastolic pressures slightly decreased

Normal contraction of the heart was demonstrated by cinefluoro-copy and als or pericardial calcifications were seen An angiocardiogram showed a sl ghtly increased d stance between the right trial cavity and the right heart border and also between the left entricular ca ty and the left heart border The-e angiographic findings were f lt to be consi tent w th mall pericardial ef fusion. The internal natom of the left ventricle ppeared normal nd w not uggestive of left entricular hypertroph

The patient w f lt to ha a restrict ve ca diomyopath of k ow tiology with moderate cardiac f ilure and small pericardial effusion. She wa giv digitalis, her dyspnea bated, nd

Table I Results of initial cardiac catheterization

	Patient	With ouabain (mm Hg)	Normal
Right trial pressure mean)	15		<5
Left trial pres ure (mean)	17		<12
Right ventricular pressure	30/15		
Left ventricular end diastolic pressure	15-17	12 13	<12
Pulmonary artery pressure (me n)	23	20	<20

Table II Results of cardiac catheterization one year after mediastinal radiation

	Rest (mm Hg)	Exercise
Right atrial pressure (mean)	2	10
Indirect left atrial pressure (mean) (pulmonary wedge)	5	
Right entricular pressure	20/2	56/10
Pulmonary artery pressure	22/5 (mean=10)	50/13 (mea =26)

she wa discharged on Dec. 11 1964 Her re included a mai tenance dose of 0 1 mg of dig every second day diphenylhydantoin, phe bital, and salt restriction.

She remained asymptomatic until Ja 1965 when she complained of right anterior ch pain of sudden onset, which radiated to the ri shoulder increased w th deep inspiration, nd associated with dyspnea and blood-streaked sp tum. Findings upon physical examinatio we unchanged f om those recorded in Octobe l except for d llness and a decrease in breath sou t the right lung base. Roentgenograms of the ch demonstrated right pleural effusion. A cl diagnosis of pulmonary infarction was str suspected. Thoracentesis produced straw-col pleural fluid of specific gravity 1 016. Bact cultures cultures for Mycobacterium tubercu and a cell-block examination of the fluid pro neg tive res lt as did phlebograms of the lower e tremities. Skin tests for histoplasmosis, blasto cosis, coccidioidomycosis trichinosis, and mu were all negative. Gastric aspirates were neg for acid-fast bacilli. Results of a liver biopsy, d because of persisting hepatomegaly were nor Electrocardiographic changes varied from at atrial fibrillation to trial flutter with 2:1 1 block.

The patient was treated with heparin, and a d tional digitoxin wa required to control cong tive cardiac failure. She improved slowly and a the time of discharge on Feb. 23, 1965, she had minimal pleural effusion. Persistent hepatomeg however was unexplained.

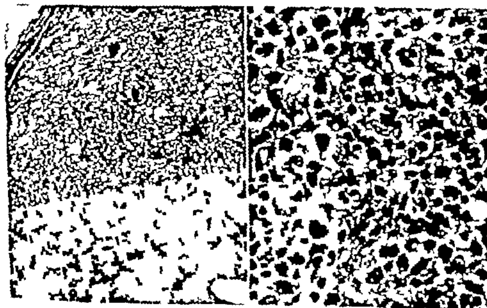
In M y 1965 she was again hospitalized beca of increasing dyspnea On physical examinat the pulse was irregular at 130 per minute, the bl pressure was 110/70, with 10 mm. Hg paradox and the respiratory rate was 30 per minute Th central venous pressure was markedly elevated a was increased by deep inspiration. The jugul venous wave form was that of restrictive peric Dullness, diminished breath sounds, and egopho were present at both lung bases posteriorly. The was considerable enlargement of the heart Hea sounds were distant and a soft third heart soun was heard at the pex. The liver edge was felt at th anterior superior spine of the right iliac crest. Th spleen tip was now palpable t the left costal m gin. There was 2+ pretibial edema. Chest roe genogram demonstrated cardiomegaly pleural e f sion and a questionable density in the ri superior mediastinum (Fig 1). After injectio carbon dioxide increased distance was ag seen between the right atrial ca ity and the ri heart border compat ble with the presence of pe cardial effusion. Thoracentesis produced a tra date. The patient was treated with a low so diet, digitoxin, chlorothiazide potassium ch supplements, and mercaptomerin She responded w with considerable regression of symptoms, he size and pleural eff sions, and as discharged o June 1 1965.

I August, 1965 routine roentgenogram of th chest demonstrated reaccumulation of pleu effusions bilaterally nd the presence of a promin right upper mediastinal mass Shortly there

was readmitted because of dyspnea t rest and le swelling On physical examination, the pulse was 64 per minute and irregular the blood sure was 110/70 without paradox the neck ere markedly distended and the harac te internal jugular pulse had disappeared. diac findings were nchanged. The liver was palpated t the iliac crest and the spleen felt 3 cm. below the left costal margin. Marked ibial pitting edema was present Electrocardio- hic findings included sinus rhythm fir t-degree rt block, and periods of sinus arrest followed by al escape beats. Because of these finding dign- was stibbeld and she was cautious! treated diuretics, thoracentesis as needed, bed rest, low-salt diet. She gradually lost 7 kilograms eight, but she remained in moderate congestiv t failure during most of her long hospitalization could toler t only limited ambulation because of the mediastinal mass and appearance plenomegal a right scalene node biopsy as ormed. Atypical lymphoid hyperplasia w d, hich as felt to be either secondary t enylhydantoi therapy or possibly ma tion of l mphoma. Diphen lh dantoin as ontinued and the patient as discharged and racted to take digitoxin, chlorothiazide spi- olactone potassium chloride and phenobarbital, h the aim of re-evalu ting the lymphatic problem several month At discharge m bradi lia with prolonged P-R interv l as present he electrocardiogram.

While at home, the patient remained orthopneic severe exercise intolerance and, on Feb 6 as readmitted for the fifth time The pulse as 48 per minute nd regular and the blood pressure as 100/60 The face appeared somewhat suffused. The retinal ein were engorged, and the neck veins were ga markedl distended without evident pulsation Small movable nontender axillary nodes ere felt There ere bilateral pleu l effusions and cardiomegaly as before The liver edge was 10 cm. below the right costal margin and the spleen tip as 4 cm below the left costal margin The abdominal veins er distended below the umbilicus nd drained inferiorly There was no edema.

Results of hemogram urinaly s nd test of blood urea nitrogen creatinine icteric index and serum glutamic oxalacetic transaminase ere nor mal The lkaline phosphatase a Bodansk u ts and the uric acid as 6 8 mg per cent P o- tein lectrophoresis showed lbumin, 3 2 g ams per cent increased α and α₂ globulin normal β nd γ globulins Coombs test latex fixation nd test for ntinuclear factor ere all negativ The esult of imm noelectrophoresis were normal Elect o- cardiogram demonstrated third-degree heart block with nodal rh thm The patient treated h chlorothiazide spironolactone mercuh drin nd salt restriction. After one month she was sympto- matically improved, nd the heart had decreased in size although there had been no appreciable eight loss On April 8 1966 there were t o epi- sodes of diaphoresis ith tingling sensation of the entire bod associated ith slow nodal h thm t rate of 25 per minute An ttempt t insert a transvenous pacemaker was unsuccessf l because of superior vena caval obstruction onfirmed by injection of H paque Sublingual isoproterenol 15 mg every 2 hours produced an increase in hea t rat t 40 per minut The adiation ther pist



 4 H mg appearance of the right postcervical node excised in August, 1966. Left panel X40 right pa 400. Note the loss of normal nodal architecture and the nuclear pleomorphism and pyknosis.

advised prompt irradiation of the right superior mediastinal mass including the heart with th field A total of 4 000 wa dm i tered

The odal hythm persisted however the rat increased to 45 t 50 per min t w thout isoproterenol and the rhythm subsequently reverted t trial fl tter fibrillation w th a entricular rate of 55 t 60 per minut The patient was discharged approximately three week after completion of therapy The perior medast nal mass regressed subsequently and during the next year the left pleural effusion disappeared and only minimal right pleural eff ion remained The mptoms and findings of cardiac f il re largely resolved

On Aug 8 1966 a 2 by 1 cm nontender firm, isolated right posterior cal nod was noted and excisional biopsy revealed the presence of highly naplastic maligna t lymphoma of reticul m cell type (Fig 4)

In order t assess more precisely th patient present cardiac st tus l mited repeat cardiac catheterization w performed in J ne, 1967 p prox mat l one ea following mediastinal radia tion The tip of th catheter in the right trium could be passed t the right heart border indicating virtual disappearance of pericardial fl id The hemod namic data re show in Tables I and II and in Fig 5 Both mean right trial and indirect left atrial (p lmonary wedge) pressures were normal t rest The dip-platea bnormal ty was no longer demonstrated in the right ventricular pressure pulse However the resting cardia output was till subnormal (2 0 L per min te per square meter) W th exercise the mea right trial pressure nd right entricular end-diastolic pressures rose to 10 mm Hg The findings indic ted that therapy had resulted in considerable improvement, b t that some degree of ventricular d sf nction remained

The patient has ince remained ery well, w th out progression of the lymphoma or deterioration i the cardiac status. She can now w lk 3 flights of stairs without dyspnea, nd is abl t do ll routine housework The ce tral enous pressure is normal and there is no edema. H patosplenomegaly persists, but there is no lymphadenopathy no nodule

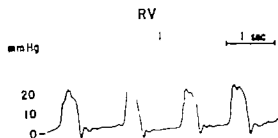


Fig 5 Right ventricular pressure pulse recorded at catheterization one yea following radiation therapy on June 22 1967 The resti g pressures are normal and the dip-plateau abnormality has disappeared from these curves which were recorded t rest.

and no evidence of hypermetabolism. Medic now include dig toxin, aldactone, and chlorothiazide, and she follow only salt-restricted diet.

Discussion

When this patient was first seen, clinical impression was that she had eith a restrictive cardiomyopathy or constrictive pericarditis. Neither the pat history nor the physical findings permi a clear differentiation.

The original hemodynamic observa did not distinguish between thes processes. While the fluctuation of heart pressures with respiration would indicate constrictive pericarditis,[3] the equality of left and right atrial pressu favored that diagnosis. As in the ca recent experience gained with restric cardiomyopathy has demonstrated it is often impossible to distinguish process, hemodynamically from constri tive pericarditis.[4] Angiocardiographi provide helpful information in this pati the increased distance between the atrial cavity and the right heart bor noted at angiography was strong evide that the pericardium contained eith tumor in retrospect or fluid at the t the patient was first studied. While distance seemed too great to be expla on the basis of simple constrictive pe carditis, it did not seem great enough explain all of the findings on the basi isolated pericardial effusion.

The patient's subsequent course nated constrictive pericarditis from co sideration The striking increase in h size which developed between Febru 1965 and May 1965 (Fig 1), al certainly would not have occurred h pericardial constriction been present. Th increase in heart size could have been either to cardiac dilatation or to pericard effusion or possibly to both. If it had be due to pericardial effusion resultin pericardial involvement with tumor seems very unlikely that the heart would have returned to near normal August 1965 after treatment for car failure alone This sequence of events gether with the development of A V strongly suggests that myocardial (in dition to possible pericardial) involvem

th tumor occurred in this patient. In dition the improvement in cardiac ction documented at the second cardiac heterization and the conversion from rd-degree A V block to atrial flutter rillation following radiation therapy pport this contention. However until tologic proof is in hand these data st be regarded only as strongly sug stive.

Whether the patient s sister suffered m a similar process is fascinating to sider but must remain speculative. Myocardial involvement with lymphoma n occur by extension from the peri rdium or from lymphatic bronchomedi inal channels, although the possibility in situ occurrence or hematogenous tastasis exists. Brick and Greenfield 1946 made the antemortem diagnosis myocardial involvement with reticulum l sarcoma in two patients, one of whom d third degree heart block.[7] Subse- ently ten cases of myocardial involve nt with lymphoma diagnosed clinically re reported in the literature and all were bstantiated by postmortem examina n. Hanfling[8] reported the autopsy find s in 85 patients with lymphoma col ted during a 7 year period and noted a per cent incidence of myocardial in lvement. Similarly Madianos and Sokal und the heart to be involved with lym oma in a large series of patients stud ed postmortem examination. Although myo- rdial *involvement with lymphoma is* quently described the number of pa nts with clinically evident cardiac dys- nction is rather small Thus far the case ports of only eight patients whose initial sentation has been with myocardial sfunction have appeared n the litera re.[10,11]

There have been relatively few reports successful treatment of infiltration of e heart with lymphoma Transitory lief has been obtained in a number of ses following radiation therapy [11] The resent patient s tumor was sensitive to radiation, which produced diminution the mediastinal mass, relief of superior ena caval obstruction and marked im rovement in the cardiac status. The long mission in clinically evident cardiac ysfunction following radiation in this case is impressive and appears to be un usual Of particularly great interest is the hemodynamic evidence of regression in the restrictive cardiac process following ther apy

Summary

A case of reticulum cell sarcoma with restrictive cardiomyopathy is reported The patient was examined because of increasing dyspnea and fatigue Cardiac evaluation including cardiac catheteriza tion demonstrated that a restrictive car diac process was present. The patient initially responded to digitalis, but even tually developed cardiac enlargement, third degree A V block and more severe cardiac failure. Superior vena caval obstruction developed as a result of right superior mediastinal lymphadenopathy Scalene node biopsy initially showed atypical lymphoid hyperplasia. After a course of radiation therapy the caval obstruction was relieved the heart block disappeared and the symptoms and signs of cardiac failure regressed A subsequent biopsy of a cervical lymph node showed anaplastic reticulum cell sarcoma. Repeat cardiac catheterization one year after radiation therapy demonstrated substantial resolu tion of the restrictive process. Up to the time of writing i.e 18 months after ther apy she continues to feel well, and she is able to do all of her housework.

The authors acknowledge the assistance and interest of the many physicians wh have been involved in the care of this patient. Special thanks are due to Drs. Paul N Y and Richard F Bake- meier for reviewing the manuscript, to Dr Roger Terry for reviewing the histopathology and t Miss Maureen Bishop and Miss Cynthia Stebbins for secretarial assistance.

REFERENCES

1 Good in, J F Gordon, H., Hollman, A., and Bishop, M B. Clinical aspects of cardiomy- opathy Brit. M. J 1:69 1961.
2. Ny R E., Lovejoy F W J and Yu, P N Clinical nd hemodynamic studies of myo- cardial fibrosis, Circulation 16:332 1957
3. Wood P Chronic constrictive pericarditis, Am. J Cardiol. 7:48, 1961
4 Yu, P N Cohen J Schreiner B F J and Murphy G W Hemodynamic alterations i primary myocardial disease Progr Cardiovas. Dis. 7 125 1964.
5. DeLoach, J F and Haynes, J W tumors of heart and pericard

subject and report of 137 cases Arch. I t Med. 91:224 1953.

6 Brucker E. A J od Glassy F J Primary *reticulum cell sarcoma of the heart with review of the literature*, Cancer 8:921 1955

7 Brick, I B and Greenfield, M Reticulum cell sarcoma with cardiac metastasis, Am. Heart J 34:599 1947

8. Hanfling S. M M tastatic cancer to the heart Circulation 22:474 1960.

9 Madianos, M and Sokal, J E. Cardia in-volvement in lymphosarcoma and [illegible] cell sarcoma, Am. Heart J 65:[illegible]

10. Nabarro, J D N Cardiac involvement in *malignant lymphoma*, Arch. Int. Med [illegible] 1953

11 Garvin, C. F Hodgkin's disease of heart and pericardium J A. M A. 117 1876, 1941.

12. Robert W C. Glancy D L, and De V T: Heart in malignant lymphoma, Am J Med. 22:85 1968.

The clinical use of diphenylhydantoin (Dilantin) in the treatment and prevention of cardiac arrhythmias

Richard H Helfant M D
George W Seuffert M.D
Robert D Patton M.D
Emanuel Stein M.D
Anthony N Damato M.D
Staten Island N Y

Although several recent clinical stud ies[1-4] have demonstrated the ef tiveness of diphenylhydantoin as an tiarrhythmic agent, its range of thera utic usefulness has not been ascertained perimental studies performed in our oratory have indicated that diphenyl dantoin may be useful in several clinical uations which have heretofore not been aluated. In addition the toxic effects intravenous diphenylhydantoin have t been adequately studied and it has en recently pointed out that continued perience with this drug is required to rmit maximum clinical effects with the nimum number of untoward responses. [7] e purpose of this paper is to present r experience with diphenylhydantoin n e prevention and treatment of cardiac rhythmias in a variety of clinical settings. part of this experience has been re rted

Methods

Diphenylhydantoin was evaluated in ur groups of patients.

Group 1 Seventy-one arrhythmias were treated with intravenous diphenylhydan toin. The drug was diluted in propylene glycol solvent and slowly infused at a rate of 25 to 50 mg per minute to a total initial dose of 5 mg per kilogram with continuous electrocardiographic and blood pressure monitoring If there was no immediate response of the arrhythmia after the initial dose, no further drug was given If the electrocardiogram demonstrated a favor able although incomplete response to the initial dose of the drug an additional 100 mg was infused at a rate of 25 mg per minute When an arrhythmia responded favorably to diphenylhydantoin an ad ditional 100 mg was given intramuscularly Thereafter the patient received 400 mg diphenylhydantoin daily in divided doses administered intramuscularly or orally This maintenance dose was discontinued as indicated by the clinical situation of each patient.

In this group a patient was classified as having responded to diphenylhydantoin if the drug resulted in (1) complete and

From the Cardiopulmonary Laboratory United States Public Health Service Hospital, Staten Island, N Y
This work was supported in part by the Bureau of Health Services, Division of Direct Health Services Project Py 64-1.
Received for publication June 6 968

permanent correction of the arrhythmia (2) complete but transient correction of the arrhythmia which then responded permanently with additional diphenylhydantoin and (3) a reduction of 75 per cent or greater in the ectopic beats.

Group 2 In 12 patients with ventricular arrhythmias, diphenylhydantoin was administered after an intravenous infusion of 750 to 1 000 mg of procaine amide had been given without restoration of sinus rhythm In four cases, procaine amide had to be discontinued because it produced widening of the QRS and or hypotension In 2 patients, neurotoxicity had necessitated stopping the drug Diphenylhydantoin was administered as in Group 1

Group 3 Twelve patients undergoing cardioversion were given 5 mg per kilogram intravenous diphenylhydantoin (administered as in Group 1) immediately prior to the procedure Five patients had developed either atrial fibrillation or atrial flutter with a rapid ventricular rate during digitalization in the hospital Three patients had developed atrial fibrillation while on maintenance digitalis therapy Three patients with atrial fibrillation developed ventricular premature beats [illegible] digitalis was being given to control [illegible] ventricular rate. One patient with a [illegible] of several episodes of digitalis [illegible] entered the hospital with ventricular [illegible]cardia.

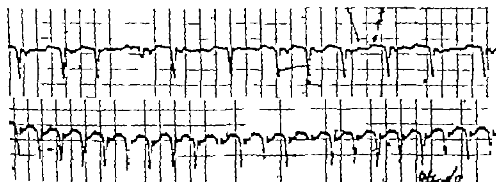
Group 4 This group consisted of [illegible] patients Eleven patients undergoing [illegible] inguinal hernia repair were given 5 [illegible] per kilogram of intravenous diphenylhydantoin at a rate of 50 mg. per [illegible] immediately prior to being anesthetized with cyclopropane. The nature and purpose of the study was explained to the patient and consent was obtained [illegible] patients served as controls, receiving [illegible] equivalent amount of Ringer's [illegible] (5 patients) or propyleneglycol [illegible] for diphenylhydantoin (4 patients) [illegible] of these patients were in sinus rhythm prior to anesthesia. Diphenylhydantoin was also given to 10 patients who developed cardiac arrhythmias during [illegible]thane, methoxyflurane or cyclopropane anesthesia not responding to standard treatment i e discontinuing the anesthetic agent increasing ventilation, [illegible] cessation of surgical stimulation. In [illegible]

Table I Effect of diphenylhydantoin in treatment of arrhythmias

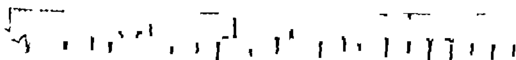
Arrhythmias	Etiology: Digitalis — No. cases	Digitalis — No. responses	Not digitalis — No. cases	Not digitalis — No. responses
I Supraventricular				1
PAT	5	3	4	
PAT with block	1	1	–	[illegible]
Flutter	2	1	6	[illegible]
Fibrillation	–	–	7	
PAF	2	1	–	[illegible]
PAC	1	0	3	–
Total	11	6	20	1
II Ventricular				3
Unifocal VPC	6	5	7	1
Multifocal VPC	9	7	3	1
Bigeminy	7	7	3	[illegible]
Vent tachycardia	2	2	3	–
Total	24	21	16	5

nts, diphenylhydantoin was administered intravenously in 50 mg doses over ds with one to two minutes between doses until the arrhythmia was terminated or a 5 mg per kilogram was reached.

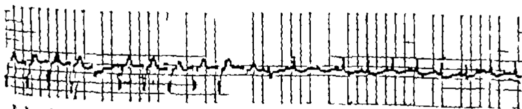
Effect of diphenylhydantoin treatment ... ardiac arrhythmias The results of ...enylhydantoin therapy in this group ...atients are summarized in Table I ... response obtained with the use of ...enylhydantoin differed depending upon ... the arrhythmia was of a supra... ...cular or ventricular origin and also ...er the arrhythmia was digitalis-induced. In the treatment of supraventricular arrhythmias that were considered to be digitalis-induced 6 of the 11 patients treated with diphenylhydantoin reverted to sinus rhythm (Fig 1) However only one of 20 patients with supraventricular tachycardia not caused by digitalis responded to diphenylhydantoin. Of these 13 patients were in atrial flutter or fibrillation and none was converted to sinus rhythm (Table I) Diphenylhydantoin did slow the ventricular rate in 6 patients and caused transient slowing of the ventricular rate in 4 patients with atrial flutter or fibrillation. None of the four patients with premature atrial contractions responded to diphenylhydantoin



Paroxysmal ...trial tachycardia developed in a patient being digitalized. Diphenylhydantoin administra... 5 mg per kilogram) converted the arrhythmia to ...sinus rhythm with ... ndering ...trial pacemaker which became a completely regular sinus rhythm after 2 minutes.



2 M...ltiple ventricular extrasystoles due t... digitalis toxicity reverted t... regular sinus rhythm 15 seconds diphenylhydantoin administration (5 mg per kilogram).



3 A patient ...ith digitalis-induced ventricular tachycardia reverted to regular sinus rhythm 15 seconds treatment ...th diphenylhydantoin (5 mg per kilogram)

In the treatment of ventricular arrhythmias, 21 of 24 patients, whose arrhythmias were considered to be caused by digitalis, responded. In this group 18 patients had either multifocal ventricular premature beats, ventricular bigeminy or ventricular tachycardia and all but two responded (Figs. 2 and 3). In contrast, only 5 of 16 patients whose ventricular arrhythmias were not caused by digitalis responded. Only 2 of 9 patients of the latter group with multifocal ventricular premature contractions, bigeminy or ventricular tachycardia responded. The differences in response to diphenylhydantoin between digitalis induced arrhythmias and those not caused by glycosides were statistically significant ($p < 0.01$).

II. Effect of diphenylhydantoin on arrhythmias after procaine amide. The results of diphenylhydantoin treatment [illegible] group of patients are summarized [illegible] II. In 9 of the 12 patients, procaine [illegible] therapy was stopped because of [illegible] QRS widening, hypotension, [illegible] or in one case, an apparent [illegible] the arrhythmia (Fig 4). In 10 of these cases, diphenylhydantoin [illegible] significantly improved the cardiac rh[illegible] by either completely abolishing the ven-tricular ectopia or decreasing their [illegible] dence substantially to the point where further treatment was considered [illegible] sary (Fig 4). In one patient, [illegible] procaine amide caused widening of the QRS; diphenylhydantoin restored [illegible] rhythm but further widening of the QRS occurred resulting in a left bundle branch block which persisted after all anti-rhythmic therapy had been stopped. [illegible]

Table II. Effect of diphenylhydantoin on arrhythmias after procaine amide

Case	Rhythm	Etiology	Procaine amide: Dose (mg)	Procaine amide: Rhythm	Procaine amide: Toxicity	Diphenylhydantoin: Dose (mg)	Diphenylhydantoin: Rhythm	Diphenylhydantoin: Toxicity
1	Ventricular tachycardia	Myocardial infarction	1,000	RSR runs of VT	Widened QRS, hypotension	400	RSR	Vert[illegible]
2	AF bigeminy	Digitalis	1,000	Incr VPC	None	450	AF	Vert[illegible]
3	Ventricular tachycardia	Arteriosclerotic heart disease	750	Unchanged	Widened QRS	500	RSR with LBBB‡	Vert[illegible]
4	VPC	Arteriosclerotic heart disease	1,000	Incr VPC	Incr VPC	350	RSR	[illegible]
5	VPC	Digitalis	750	Unchanged	Dizziness, nausea	300	Decr VPCs	[illegible]
6	VPC	AS, AI	750	Unchanged	Hypotension	350	Decr VPCs	Vert[illegible]
7	Multifocal VPC	Digitalis	750	Incr VPC	Widened QRS	300	RSR	Vert[illegible]
8	Ventricular tachycardia	Pul. emboli	1,000	Unchanged	? Confusion, ? hypotension	500	Unchanged	Vert[illegible]
9†	Ventricular tachycardia	Pul. emboli	750	Unchanged	Hypotension, widened QRS	350	Unchanged, narrower QRS	Vert[illegible]
10	AF VPC	Digitalis	750	Incr vent. rate VPC	None	350	Decr vent. rate decr VPC	[illegible]
11	VPC	Arteriosclerotic heart disease	1,000	Decr VPC	Agitation, confusion	250	Decr VPC	[illegible]
12	AF VPC	Digitalis	750	Unchanged	None	330	Decr VPC	Vert[illegible]

*Patient died. (See results.)
†Patient successfully cardioverted.
‡See text for discussion of this case.

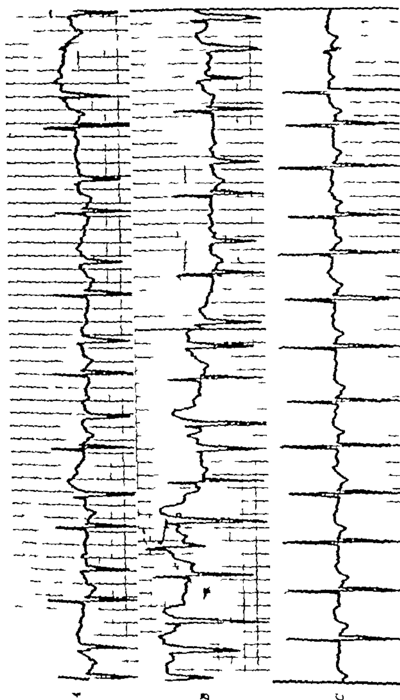


Fig. 4. A. Ventricular bigeminy due to digitalis toxicity in a patient with chronic atrial fibrillation. B. After 1,000 mg. intravenous procaine amide the ventricular extrasystoles increased in number and became multifocal. C. 30 seconds after diphenylhydantoin (5 mg. per kilogram) the patient reverted to atrial fibrillation with no ventricular extrasystoles.

persistence of the bundle branch block would suggest that it was not due to drug therapy. In another patient with pulmonary emboli and ventricular tachycardia the QRS widened after procaine amide. Although diphenylhydantoin narrowed the QRS complexes the ventricular tachycardia persisted and DC countershock finally established sinus rhythm. An additional patient with pulmonary emboli and ventricular tachycardia went into shock during procaine amide infusion. Diphenylhydantoin did not affect the rhythm and the patient died two hours later.

III. Prophylactic diphenylhydantoin before DC countershock. In the 12 patients who were pretreated with diphenylhydantoin DC countershock produced regular sinus rhythm with no immediate po[illegible] arrhythmias. In 8 cases, pretreatment [illegible] diphenylhydantoin was instituted be[illegible] of the development of atrial flutte[illegible] fibrillation either during digitaliz[illegible] patients) or while on maintenance [illegible] therapy (3 patients). In these pat[illegible] diphenylhydantoin did not change [illegible] atrial arrhythmia although slowing of t[illegible] ventricular rate was noted in 5 cases. [illegible] patient developed ventricular prema[illegible] contractions 2 hours after countersh[illegible] which were abolished with an additi[illegible] 100 mg of diphenylhydantoin given int[illegible] venously. In the three patients with [illegible] fibrillation in whom ventricular prema[illegible] contractions developed while digitalis [illegible] being instituted diphenylhydantoin ad[illegible] ministration abolished the premature [illegible]

Table III. Effect of prophylactic diphenylhydantoin on development of arrhythmias d[illegible] cyclopropane anesthesia

Ailment	Induction		Maintenance	
	Diphenylhydantoin	Control	Diphenylhydantoin	Control
No arrhythmia	8	2	10	[illegible]
PVC	0	3	0	[illegible]
Bigemini	3	2	1	[illegible]
Ventricular tachycardia	0	2	0	[illegible]

Table IV. Effect of diphenylhydantoin in treatment of arrhythmias during anesthesia

Case	Anesthetic	Arrhythmia	Dose of diphenylhydantoin (mg.)	Result
1	Halothane	Multifocal PVC's, trigeminy	350	RSR
2	Methoxyflurane	PVC, trigeminy	250	RSR
3	Halothane	Vent. tachycardia	150	RSR
4	Halothane	Bigeminy	200	RSR
5	Halothane	Wandering pacemaker	400	No effect
6	Nitrous oxide	AV dissociation	450	No effect
7*	Nitrous oxide	Atrial flutter, multifocal PVC	200	RSR
8	Cyclopropane	PVC	250	RSR
9	Cyclopropane	PVC	250	RSR
10	Cyclopropane	PVC	350	RSR

*After diphenylhydantoin, blood pressure dropped from 110/70 to 90/60, but spontaneously returned to initial value after 5 [illegible]

ll instances and slowed the ventricular in two patients. DC cardioversion red regular sinus rhythm with no pac beats in all cases. One patient on ing digoxin daily in whom the etiorole of digitalis was not clear entered hospital with ventricular tachycardia enylhydantoin did not affect the ar hmia and DC countershock promptly red sinus rhythm with no ectopic s.

Effect of diphenylhydantoin during al anesthesia

OPHYLACTIC DIPHENYLHYDANTOIN DUR CYCLOPROPANE ANESTHESIA. The re of prophylactic diphenylhydantoin ng cyclopropane anesthesia are seen able III. Whereas only one of the nine nts in the control group was free of ythmias, eight of the 11 patients who pretreated with diphenylhydantoin not develop arrhythmias during the e anesthetic. Furthermore during the ntenance phase of anesthesia, only one he patients in the control group was of arrhythmias whereas 10 of the 11 ents pretreated with diphenylhydan had no arrhythmias. This difference atistically significant ($p < 0.01$). The groups had similar blood gas and pH es during anesthesia.

FECTS OF DIPHENYLHYDANTOIN TREAT T DURING GENERAL ANESTHESIA. Di nylhydantoin restored sinus rhythm ll 8 patients who developed ventricular ythmias during the administration of ous anesthetics (Table IV). In two ents with supraventricular arrhyth s, diphenylhydantoin had no effect.

Diphenylhydantoin toxicity. In all s, side effects due to diphenylhydan therapy were minor and transient. deaths occurred which were causally ted to diphenylhydantoin administra In one patient the arrhythmia apred to have been made worse by diphen dantoin. This patient was in egular s rhythm with ventricular premature tractions which increased after 100 mg avenous diphenylhydantoin had been n. A cessation of all medications lead restoration of sinus rhythm in 2 days. 5 patients, a mild fall in blood pressure to 20 mm. Hg systolic) occurred which ll cases returned to the baseline level in several minutes without treatment. Other side effects included pain at the site of injection nausea lightheadedness, drowsiness, dizziness, and nystagmus. These symptoms were uniformly minor and transient. No toxic effects were seen when diphenylhydantoin was given prophylactically before anesthesia or prior to DC cardioversion.

Discussion

In several recent clinical reports, diphenylhydantoin has been demonstrated to be a useful antiarrhythmic agent, especially in the treatment of cardiac arrhythmias caused by digitalis excess. In the present study diphenylhydantoin's effectiveness in treating ventricular arrhythmias induced by digitalis was most impressive and is in agreement with the findings of others.[4] Eighty-five per cent of patients in whom the ventricular arrhythmia was related to digitalis excess showed a response to the drug either during or within 5 minutes after completion of the infusion. Several of these patients had either multifocal premature beats (Fig. 2) or ventricular tachycardia (Fig. 3) while others had bigeminal rhythms. On the other hand only 27 per cent of ventricular arrhythmias which were not induced by digitalis responded to diphenylhydantoin.

The relative ineffectiveness of diphenylhydantoin in atrial arrhythmias not induced by digitalis has been noted by others and confirmed in the present report. Only one supraventricular arrhythmia not caused by digitalis responded to diphenylhydantoin. In addition only one of 8 patients with atrial flutter and none of the 7 patients with chronic atrial fibrillation reverted to sinus rhythm although the ventricular rate was decreased in ten patients. Thus, it would appear that diphenylhydantoin has no place in the conversion of atrial flutter or atrial fibrillation to sinus rhythm, although it may be useful in slowing the ventricular rate in these circumstances.

In the group of patients with ventricular arrhythmias unresponsive to procaine amide, diphenylhydantoin was of considerable value. In 10 of these patients, with either multiple premature beats or ven

tricular tachycardia the ectopia were either completely abolished or their frequency markedly reduced (Fig 4) The results in this group of patients provide further clinical evidence that diphenylhydantoin may be of value in correcting ventricular arrhythmias that respond to procaine amide. Experimentally diphenylhydantoin reverses the conduction prolongations produced by procaine amide while additively depressing ventricular automaticity [8]

Diphenylhydantoin has been used prophylactically in several situations. Berstein and co-workers[9] reported that prophylactic oral diphenylhydantoin is beneficial in patients with recurrent cardiac arrhythmias, a finding that has more recently been confirmed by Mercer and Osborne

In dogs undergoing DC countershock prophylactic diphenylhydantoin greatly increased the amount of electrical energy required to produce an arrhythmia after digitalis infusion had markedly decreased the arrhythmogenic energy threshold [8] In the present study none of the patients who were pretreated with diphenylhydantoin prior to DC cardioversion developed immediate postshock arrhythmias. There is no way of knowing whether postshock arrhythmias would have developed in this group of patients had diphenylhydantoin not been given However a consideration of the preceding circumstances and the excellent results obtained lead us to judge that under the clinical conditions described the prophylactic use of diphenylhydantoin was of value. This correlates with the findings of Mercer and Osborne[4] and others[7] that arrhythmias which occur after cardioversion respond well to intravenous diphenylhydantoin

Another situation which is associated with a high incidence of cardiac arrhythmias is general anesthesia. In a recent study the incidence of significant arrhythmias during general anesthesia and surgery was found to be 61 7 per cent.[11] Most of these arrhythmia can be abolished by correcting technical factors such as airway obstruction hypoxia hypercarbia and acidosis. However some arrhythmias persist especially in patients with cardiac disease [13] In the present series of patients, only one of the 9 in the control group [illegible] free of arrhythmias during general anesthesia whereas 10 of 11 patients who were pretreated with diphenylhydantoin did not develop arrhythmias. In addition diphenylhydantoin also abolished all ventricular arrhythmias that developed during general anesthesia which did not respond to standard nonpharmacologic treatment These results indicate that prophylactic diphenylhydantoin may be of value in selected patients undergoing general anesthesia.

Experimentally prophylactic diphenylhydantoin increases in dose of digitalis necessary to produce an arrhythmia by an average of 122 per cent.[11] Although preliminary evidence indicates that diphenylhydantoin can increase the "toxic-therapeutic" ratio of digitalis in [illegible] selected cases our clinical experience [illegible] present is considered too small to be included in this report.

It appears from our experience and [illegible] that of others that the prophylactic use of diphenylhydantoin may have a wider spectrum of action than in the treatment of arrhythmias once they have occurred In this regard Bashour and associates monitoring the cardiac rhythm in patients following myocardial infarction found that the group receiving prophylactic diphenylhydantoin had a significant reduction in the incidence of arrhythmias. Although the accumulated clinical experience with the prophylactic use of diphenylhydantoin under arrhythmogenic clinical situations is small It is hoped that the findings [illegible] cussed will stimulate more definitive work in each of these areas.

In our series of patients, we have had no deaths that could be ascribed to the use of intravenous diphenylhydantoin. Our experience confirms that of almost all other clinical reports which indicate diphenylhydantoin to be a relatively safe drug when used correctly However fatal [illegible] due to diphenylhydantoin have been reported [9] [14] In preventing serious toxicity the speed of injection is of paramount importance. Diphenylhydantoin should be infused no faster than 25 to 50 mg per minute with continuous electrocardiographic and blood pressure monitoring [illegible]

se circumstances, serious toxicity can kept at a minimum

n summary diphenylhydantoin appears be a valuable agent in both the treat nt and prevention of cardiac arrhyth is. Because of its rapid onset of action ative safety and effectiveness, we con er it to be the agent of choice in the atment of serious ectopic rhythms sed by digitalis toxicity

Summary

The use of intravenous diphenylhydan n (5 mg per kilogram) in the treatment l prevention of cardiac arrhythmias s studied In the treatment of arrhyth as caused by digitalis, diphenylhydan n restored 6 of 11 atrial arrhythmias sinus rhythm and 21 of 24 ventricular hythmias responded In patients whose hythmias were not digitalis-induced ly one of 20 patients with atrial and 5 16 with ventricular arrhythmias re- onded Diphenylhydantoin significantly proved the cardiac rhythm in 10 of 1? tients with ventricular arrhythmias ich were unresponsive to procaine amide. In 12 patients, atrial or ventricular ar ythmias developed either during digi lization or maintenance digitalis. In ese patients, diphenylhydantoin was ven immediately prior to DC cardio- rsion In all cases, DC countershock oduced sinus rhythm with no immediate stshock arrhythmias.

Diphenylhydantoin was given to 11 tients prior to cyclopropane anesthesia. en of the 11 patients had no arrhythmias ring the anesthetic, whereas only one 9 patients in the control group was free arrhythmias. Diphenylhydantoin re- ored sinus rhythm in 8 patients who veloped ventricular arrhythmias during e administration of various anesthetics, ut had no effect in 2 patients with atrial rhythmias.

Side effects due to diphenylhydantoin ere minor and transient and no deaths curred It is concluded that with slow dministration and careful electrocardio- raphic and blood pressure monitoring iphenylhydantoin is a saf and valuable gent n both the treatment and preven ion of cardiac arrhythmias.

REFERENCES

1 Conn, R D Diphenylhyda tol sodium in cardiac arrhythmias, New England J Med. 272:277 1965.

2. Karliner J S. I travenous diphenylhydantoin sodium (Dilantin) in cardiac arrhythmias, Dis. Chest 51:256, 1967

3 Rosen, M R Lusk R., nd R bin, I L Diphenylhydantoin in cardiac arrhythmias, Am. J Cardiol. 20:674 1967

4 Mercer E. N and Osborne, J A. The current status of diphenylhydantoi in heart disease, Ann I t. Med 67 1084 1967

5 Helfant, R. H., Scherlag B J and Damato, A N Use of diphenylhydantoi sodium t dissociate the effects of procaine amide on automaticity and conduction in the normal and arrhythmic heart, Am J Cardiol. 20:820 1967

6. Helfant, R H Scherlag, B. J and Damato, A. N Diphenylhydantoin prevention of ar rhythmias in the digitalis-sensitized dog after direct-current cardioversion, Circulation 37 424 1968.

7 Editorial Cardiac arrhythmias and sodium diphenylhydantoin—an appraisal, J.A.M.A. 201 142, 1967

8 Seuffert, G W Helfant, R. H Dana J F and Urbach K F The use of diphenylhydan- toin in the prevention and treatment of cardiac arrhythmias during general anesthesia, Anesth. & Analges. I press.

9 Bernstein, H Gold, H Lang, T W Pappel baum S Bazika, V and Corday E. Sodium diphenylhydantoin in the treatment of recur rent cardiac arrhythmias, J A M.A. 191:695 1965

10. Lang, T W Bernstein, H., Barbieri, F F Gold, H and Corday E. Digitalis toxicity Treatment with diphenylhydantoin, Arch I t Med. 116:573 1965.

11 Kuner J Enescu, V Utsu, F Boszormenyi, E Bernstein, H and Corday E. Cardiac arrhythmias during anesthesia, Dis. Chest 52:580, 1967

12. Erlanger H Cardiac arrhythmias in relation- ship t anesthesia past and present concepts, Am J M Sc. 213:651 1962

13 Helfant, R. H Scherlag B. J and Damato, A N Protection from digitalis toxicity with the prophylactic use of diphenylhydantoin sodium. A arrhythmic-inotropic dissociation, Circulation 36 119 1967

14 Bashour F A. Jones, E., and Edmonson, R Cardiac arrhythmias in acut myocardial infarction. II. Incidence of the common ar rhythmias with special reference to ventricular tachycardia, Dis Chest 51:520, 1967

15 Unger A. H., and Sklaroff H. J F talities following intravenous use of sodium diphenyl- hyda toi for cardiac arrhythmias, J A M A. 200 159 1967

16 Gellerma G I and Martinez, C. F tal entricular fibrillation following intravenous sod m diphen lhydantoi therapy J.A M A. 200 161 1967

The heart in heatstroke

Michael C. Kew, F.C.P. (S.A.)
Ronald B. K. Tucker, F.C.P. (S.A.)
Israel Bersohn, F.C.Path.
Harold C. Seftel, Dip. Med. (Rand)
Johannesburg, South Africa

Heatstroke may be defined as a state of acute thermoregulatory failure which follows exposure to high environmental temperatures and which manifests with disturbances of the central nervous system and hyperpyrexia (rectal temperature greater than 105° F.). Generalized anhidrosis is usual but not invariable.[1] Widespread tissue injury occurs as a result of heatstroke. Whereas the changes in certain organs, notably the kidney,[2] liver, and brain have been documented, little information is available on the effects of heatstroke on the heart.

The limited evidence of myocardial damage in heatstroke is based on the electrocardiographic findings in a small number of patients[?] and the pathological changes in fatal cases.[3,4] Although many of the serum enzymes are known to be elevated in patients with heatstroke,[?] no attempt has hitherto been made to determine whether these enzymes have a myocardial origin and reflect cardiac damage. The purpose of this paper is to describe the cardiac changes that occurred in 26 unselected patients with heatstroke and to assess the frequency and natural history of this complication. The study is ba[sed] on the clinical findings, serum enzy[me] and electrocardiographic changes, a[nd] where possible pathological examinat[ion] of the heart.

Clinical material and methods

The 26 patients studied were Ba[ntu] men who developed heatstroke while wo[rk]ing underground in the Transvaal a[nd] Orange Free State gold mines. The [illegible] characteristics of the Bantu miners a[nd] the environmental conditions encounter[ed] underground in the mines have been de[s]cribed in detail in a previous publicatio[n]. All the patients were healthy prior to de[]veloping heatstroke and none was [illegible]. Their ages ranged from 20 to 57 ye[ars] with a mean of 32 years. Sixteen of the patients had been fully acclimatized and the remaining 10 were undergoing a[c]climatization when heatstroke occurre[d]. The reasons for the development of heat[]stroke even in fully acclimatized worke[rs] are attributable to heavy physical la[bor] in an extremely hot and humid environ[]ment.

The serum lactic dehydrogenase (LD[H]

From the C.S.I.R. Cardiopulmonary Research Unit and the Cardiovascular Research Unit, Department of Med[icine], University of the Witwatersrand and Johannesburg General Hospital, and the South African Institute [for] Med[ical] Research, Johannesburg, South Africa.
Supported by funds from the Chamber of Mines of South Africa.
Received for publication June 10, 1968.

is measured serially in all cases and was ctionated into its isoenzymes in 16. e serum LDH was measured by the thod of Wroblewski and LaDue[3] (nor l range 100 to 280 units) LDH was ctionated by paper electrophoresis, the ctions being localized by histochemical thods and then measured using Spinco alytrol. The fraction migrating to the thode is referred to as LDH 5 The test fraction migrating to the anode is DH 1 LDH 2, LDH-3 and LDH-4 ve at progressively slower speeds. The rmal ranges for this method in our oratory are LDH 1 15 to 21 per cent ean 18 per cent) LDH 2 32 to 45 per nt (mean 38 per cent) LDH-3 23 to 31 r cent (mean 27 per cent) LDH-4 7 to per cent (mean 11 per cent) LDH 5 to 8 per cent (mean 6 per cent) The ab- lute number of units in each instance was so recorded Fractionation of the LDH in rmal human heart tissue using the same ethod has shown the following pattern DH 1 44 per cent LDH 2 40 per cent DH 3 10 per cent LDH-4 3 per cent DH 5 3 per cent. Following Wroblewski d associates[1] and others[14] an increase the percentage of LDH 1 in the serum is considered to be indicative of myo- rdial damage.

Electrocardiographic tracings were re rded in all patients. In 12 the initial electrocardiogram (ECG) was obtained within 12 hours of the onset of the illness within 24 hours in 5 and within 72 hours in the remaining 9 As miners who develop heatstroke are usually returned to their homelands after recovery long term fol low up has not always been possible. However serial ECG s were performed in 15 patients over periods ranging from 6 weeks to 4 years. Although all mining recruits are examined before being ac cepted for work on the mines, the exami nation does not include an ECG No com parison with electrocardiographic tracings prior to heatstroke was therefore possible.

Three patients died as a result of the heatstroke, and in these, myocardial tissue was available for histological examination.

Results

Clinical findings In 21 patients rectal temperatures were recorded at the onset of the illness and these ranged from 105 to 111 5° F with a mean of 107° F When first seen 10 of the patients were comatose, 8 were semicomatose, and the remaining 8 were severely or moderately confused Because the patients were cooled under ground before being brought to the surface there was a lapse of 1 to 3 hours before a full clinical examination could be carried out. Thereafter the patients were under constant medical observation. On admis-

able I *The maximum serum LDH level in 26 patients with heatstroke*

Patient no.	*Maximum LDH level (units)*	*Patient no*	*Maximum LDH level (units)*
1	1 300	14	930
	22 000	15	530
3	3 400	16	6 000
4	16 000	17*	3 500
5	900	18	1 450
6	4 000	19	1 300
7	600	20	1 850
8	1 860	21	1 150
9	4 100	22	3 200
10	3 000	23	2 100
11	7 000	24	1 270
12	1 200	25	1 410
13	6 500	26	13 700

*Denotes fatal case.

sion the systolic blood pressure was between 100 and 160 mm. Hg in 14 patients, between 80 and 100 in 5 and less than 80 in 7 The pulse rate varied from 100 to 144 beats per minute In most patients, the pulse volume was normal or increased with a hyperdynamic circulation In those patients with a low blood pressure, the pulse was of poor volume The venous pressure was not elevated in any patient and no evidence of pulmonary edema or systemic venous congestion was found Apart from an atrial sound in one patient (No. 12) no auscultatory abnormalities were detected

Of the 26 patients 23 made a complete clinical recovery id 3 died 2 in hepatorenal failure and 1 from peritonitis complicating perito ieal dialysis

Serum lactic dehydrogenase and its isoenzymes The serum LDH was elevated in all patients (Table I) The elevation appeared within 24 hours of the onset of heatstroke reached its maximum after approximatel 72 hours, and persisted for 4 to 17 days with a mean of 1 2 days.

The serum LDH was fractionated in 16 patients (Table II) In 11 the percentage of LDH 1 was significantly increased The maximum levels were usually reached 48 to 96 hours after the episode of heat- However in 6 cases the serum LDH became significantly elevated only a- 3 to 6 days had elapsed. The increased pe- centage of LDH 1 persisted for 7 to 1 days. This evidence of myocardial in- was always associated with evidence of hepatic or renal damage as judged b- increases in the percentages of LDH and LDH 2 respectively

Electrocardiographic findings. These a- summarized in Table III

Rhythm A tachycardia (pulse rate 1- to 144 beats per minute) was present i- patients shortly after the episode of h- stroke. This was shown to be a sinus tach- cardia in the 12 cases in which ECG's we- performed within the first 12 hours W- the exception of one patient (No. 11) wh- had frequent ventricular ectopic bea- during the first 24 hours no arrhythm- were detected. This miner had not h- an irregular pulse prior to developing hea- stroke and showed no further arrhythm- He died after 8 days.

Conduction No major conduction de- fects were observed

P R interval The P R interval was no- mal in all except one patient (No. 1- in whom it was prolonged to 0.28 sec

Table II The maximum serum levels of LDH 1 in 16 patients with heatstroke

Patient	Serum LDH	LDH 1		LDH-2		LDH 3		LDH-4		LDH 5	
			Units		Units		Units	%	Units	%	Units
1	670	35	218	47	292	10	62	5	31	3	[illegible]
2	700	29	203	48	336	15	105	6	42	2	[illegible]
3	1 060	25	265	46	487	18	171	6	64	5	[illegible]
4	16 000	7	1 120	28	4 480	24	3 840	20	3 200	21	[illegible]
5	550	28	154	35	192	11	60	7	38	19	[illegible]
6	950	30	285	46	437	17	161	5	47	2	[illegible]
7	500	16	80	35	175	32	160	8	40	9	[illegible]
8	1 220	34	415	48	585	11	134	3	37	4	[illegible]
9	700	30	210	46	322	15	105	5	35	4	[illegible]
10	700	31	217	39	273	18	126	4	28	8	[illegible]
11	6 500	6	420	13	910	19	1 330	23	1 610	39	[illegible]
12	1 200	26	312	43	516	20	240	5	60	6	[illegible]
13	500	[illegible]	180	41	205	13	65	5	25	5	[illegible]
14	930	14	130	40	372	28	260	9	81	9	[illegible]
15	380	14	53	29	111	25	95	12	45	20	
16	900	30	270	[illegible]	405	14	127	5	49	3	[illegible]

Denotes f tal case.

n first degree heart block was still pres-
t 5 weeks after the episode of heatstroke.
e patient showed other electrocardio-
aphic evidence of severe myocardial
mage (Fig 1)

Q-T$_c$. The Q-T$_c$ was prolonged to be-
een 0.45 and 0 54 second in 9 of the 26
tients. In 6 cases, serial tracings were
rformed and in all of the Q-T$_c$ returned
normal within 10 days. As prolongation
the Q-T$_c$ may be due to changes in the
um electrolytes, these were measured
thin several hours of the onset of heat
oke in 14 patients. The serum potassium
nged from 2 8 to 5 2 mEq per liter with
mean of 4 0. In only 2 cases was the level
low 3.5 mEq per liter The serum sodium
ried from 124 to 156 mEq per liter with
mean of 139 and the serum chloride 96
117 mEq per liter with a mean of 103 6
The carbon dioxide combining power ranged from 8 0 to 20 0 mEq per liter with a mean of 13 1 No correlation could be demonstrated between the serum electrolyte levels and the duration of the Q-T$_c$.

Mean frontal plane QRS and T wave axes The mean frontal plane QRS axis was within the normal range (0 to +90°) in all cases. The angle between the QRS and T wave axes was normal (less than 60°)[14] in 22 patients and greater than 60° in 4. This angle varied from 70 to 160° in the abnormal cases. Of these patients, one died in the acute stage and 2 were not available for follow-up in the remaining case the ECG returned to normal over a period of 5 months.

S-T segment and T-wave changes In 14 to 22 per cent of apparently normal Bantu

ble III *Summary of the electrocardiographic abnormalities and the correlation between these anges and the maximum serum level of LDH 1*

atient no.	Maximum % of LDH	Arrhythmia	P R int	Q-T	QRS/T	T wave flattening	T-wave inversion	S-T depression	S-T elevation	P wave
1	35	–	0 13	0 48	0°	+†	–‡	–	–	–
2	29	–	0 14	0 54	5°	+	+	–	–	–
3	25	–	0 10	0 37	40°	–	–	–	+	–
4	7	–	0 16	0 39	40°	–	–	–	–	–
5	28	–	0 14	0 39	30°	+	–	–	–	–
6	30	–	0 12	0 42	10°	–	–	–	–	–
7	16	–	0 14	0 44	20°	–	–	–	–	–
8	44	–	0 16	0 45	50°	+	+	–	–	–
9	30	–	0 13	0 38	20°	+	–	–	–	–
10	31	–	0 16	0 47	30°	–	–	–	–	–
11	6	–	0 12	0 45	160°	+	+	+	–	+
12	26	–	0 28	0 46	150°	–	+	–	–	+
13	36	–	0 12	0 48	20°	+	+	+	–	+
14	14	–	0 14	0 39	20°	–	–	+	–	–
15	14	–	0 14	0 44	10°	–	–	–	–	–
16	30	–	0 14	0 41	40°	+	–		–	–
17*		+	0 14	0 42	30°	+	–	–	+	–
18		–	0 13	0 49	90°	+	+	–	–	–
19		–	0 18	0 39	60°	+		–	–	–
20		–	0 18	0 43	60°	–	–	–	–	–
21		–	0 16	0 38	25°	–	–	–	–	–
22		–	0 16	0 38	70°	–	–	–	–	–
23		–	0 14	0 39	30°	–	–	–	–	–
24		–	0 21	0 44	20°	–	–	–	–	–
25		–	0 16	0 42	20°	–	–	–	–	–
26		–	0 14	0 47	5°	+	–	–	–	–

*Denotes fatal case.
†Stands for positive.
‡Stands for negative.

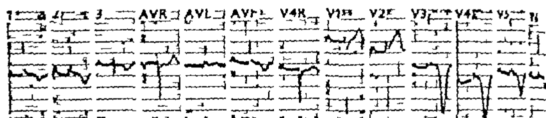


Fig 1 ECG (Case N[illegible] 12) showing first degree heart block (P-R interval 0.28 second) and deeply inverted [illegible] waves. The mean frontal plane QRS/T angle was at least 150°. The P wave in standard II is tall and [illegible]. Apart from the P[illegible] which returned to normal, the tracing was unchanged when the patient [illegible] weeks after developing heat stroke

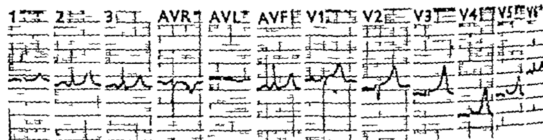


Fig 2 ECG (Case N[illegible] 15) showing S-T segment elevation associated with peaked T waves in the chest le[illegible] (B[illegible] type II pattern)

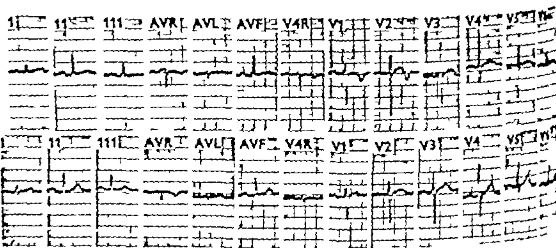
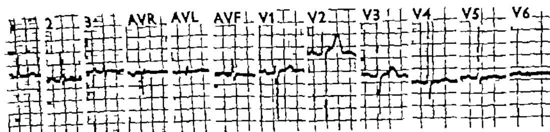


Fig 3 (A) ECG (Case No 23) 48 hours after onset of heatstroke showing pattern which resembles persistence of the juvenile pattern (Bant[illegible] type I) (B) ECG performed 4 months after the above tracing. The S-T [illegible] and T wave changes in Lead V[illegible] and V[illegible] are no longer present.

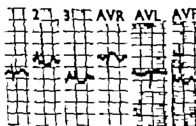
adults the S-T segment and T wave patterns differ from those seen in Caucasians.[5-8] These variants have been divided by Grusin[9] into two main categories first, persistence of the juvenile pattern in the right and mid-chest leads (type I) and second S-T segment elevation with pe[illegible] T waves, mainly in the left chest le[illegible] (type II). In the present series, there w[illegible] 3 patients who showed type II ch[illegible] alone (Fig 2). Serial tracings revealed [illegible] alteration in the pattern and these ECG[illegible]

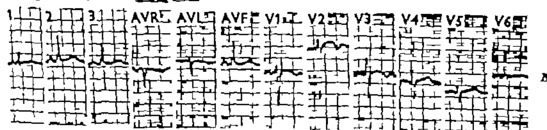


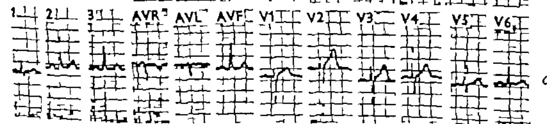
4 ECG (Case No. 19) showing flattening of the T wa es in the standard, unipolar limb and the left pre-
dial lead



3 ECG (Case No. 18) showing inverted T aves in standard Leads II and III, Lead aV and Leads V to
The S-T segment elevation in the precordial leads may be related t Bant type II pattern.







g. 6 (*A*) ECG (Case No. 13) performed 4 hours after the onset of heatstroke showing depressed S-T segments standard Leads II and III and Lead V with reciprocal elevation in Lead aV. The P e in standard Lead I is tall and peaked. (*B*) ECG t 48 hours showing disappearance of the original changes. There is now inversion f the T es in Leads V to V associated with S-T segment elevation. The T wa in Lead V is flattened. he Q-T is prolonged to 0.48 second (*C*) ECG performed after 3 eek showing increase in the amplitude f the T aves in all leads nd upright T w es in V to V. The Q-T has returned to normal (0.39 second).

were regarded as being normal. Early ECGs on 5 patients showed only type I changes (Fig 3 A) With serial tracings the inverted T waves in the precordial leads disappeared (Fig 3 B) As this has been described in Bantu with the type I pattern these ECGs were regarded as being normal

The following changes were considered to be abnormal 1 Six patients showed flattening of the T waves (Fig 4) This was usually generalized but in 2 patients it was confined to the left precordial leads. In one patient, the T waves were deeply inverted in all leads (Fig 1) and in another the T waves were inverted in standard Leads II and III Lead aV$_F$ and Leads V$_4$ to V$_6$ (Fig 5)

2 S-T segment depression in standard Leads II and III and Lead aV$_F$ was present in 2 patients 4 to 6 hours after the onset of heatstroke (Figs. 6 A and 7 A) This persisted for less than 24 hours, and was replaced by flattening or slight inversion of the T waves (Figs. 6 B and 7 B) One patient showed slight depression and straightening of the S-T segments, particularly in the mid precordial leads (Fig 8)

3 Elevation of the S-T segments was present in 2 patients. In one, it occurred in the mid and left precordial leads and was associated with generalized flattening of the T waves (Fig 9) The second showed slight elevation of the S-T segments in standard Lead III and Lead aV$_F$ (Fig 1

The S-T segment and T-wave abnormalities returned to normal in each of the patients in whom serial ECGs were performed The time taken for this to occur ranged from a few days to 4 to 5 months

Ventricular enlargement In 2 patients the depth of the S wave in Lead V$_1$ and the height of the R wave in V$_5$ or V$_6$ was suggestive of left ventricular enlargement, the sum of the voltages being 50 and 5 mm respectively However amplitudes of this order have been described in normal Bantu subjects.[29] Neither patient had clinical or radiological evidence of cardiac enlargement

P waves The P wave was abnormally tall (greater than 2 5 mm.) and peaked in standard Lead II in 3 patients (Fig 4,

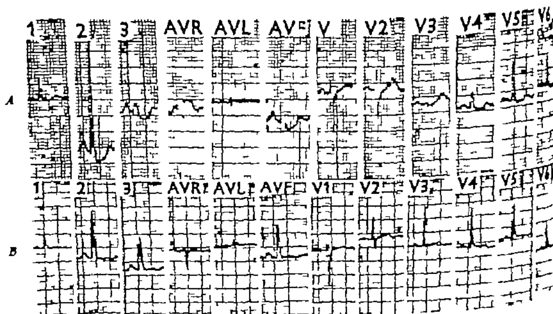


Fig 7 (A) ECG (Case No. 11) recorded 4 hours after the onset of heatstroke. There is S-T segment depression in standard Leads II and III and Lead aV$_F$ with reciprocal elevation in Lead aV (B) ECG performed 4 hours after the above tracing There is now inversion of the T waves in standard Lead II and III and Lead aV$_F$ flattening of the T waves in the other lead The mean frontal plane QRS/T angle was 160° This patient died after 72 hours.

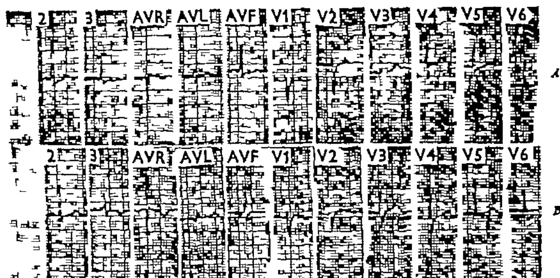


Fig. 8.—(A) ECG (Case No. 14) recorded 5 hours after the onset of heatstroke showing slight depression and straightening of the S-T segments particularly in the mid precordial leads. (B) ECG performed 4 weeks later showing return of the tracing to normal.

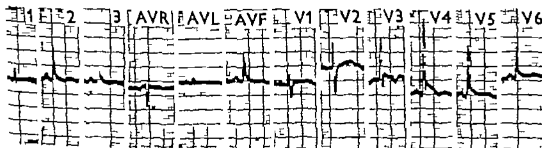


Fig. 9. ECG (Case No. 17) recorded 6 hours after the onset of heatstroke showing generalized flattening of the T waves and elevation of the S-T segments in the mid and left leads.

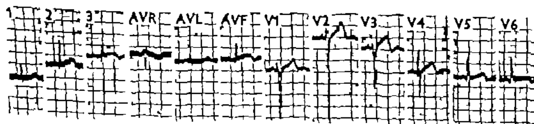


Fig. 10. ECG recorded 12 hours after the onset of heatstroke. There is slight elevation of the S-T segment in standard Lead III and Lead V associated with inverted T waves. These findings disappeared with serial tracings (Case No. 3.)

In all the amplitude returned to normal within 24 to 48 hours.

Correlation between isoenzyme and electrocardiographic changes In 16 patients both investigations were performed (Table III) In 9 both criteria of myocardial injury were positive in 3 neither was positive in 2 only the ECG was abnormal and in the remaining 2 patients the serum isoenzymes alone were elevated There was thus a 75 per cent correlation between the indices. There was no correlation between the isoenzyme level and the type of electrocardiographic change in any particular patient Nor did the patients with more than one electrocardiographic abnormality tend to have higher isoenzyme levels.

Pathological findings One patient (No. 11) died from hepatorenal failure 72 hours after developing heatstroke The ECG (Fig 7) had shown a moderate degree of myocardial damage but the percentage of LDH 1 in the serum was not elevated Macroscopic examination of the heart showed a pale myocardium with subendocardial and myocardial hemorrhages. Microscopically there was a marked degree of interstitial edema. The cytoplasm of the muscle fibers was edematous and showed disappearance of the normal cross striations and granular and vacuolar degeneration. The nuclei were often pale and swollen and in some the nuclear membrane was disrupted Chromatolysis was commonly seen

The second patient (No. 17) died in acute renal failure 8 days after the onset of his illness The myocardium showed a moderate degree of interstitial edema and focal areas of degeneration of the muscle fibers. The third patient (No 26) also developed acute renal failure and died after 26 days from peritonitis complicating peritoneal dialysis. The myocardium was normal. In both of the latter patients, ECG s recorded shortly after the onset of heatstroke had shown mild or moderate S-T segment and T wave changes The serum LDH was elevated in both these patients, but isoenzymes were not measured

Discussion

Frequency of cardiac damage The incidence of cardiac involvement in heatstroke is difficult to assess from previous rep[illegible] and in only a few have the electroc[illegible] graphic findings been discussed.[illegible] Nevertheless S-T segment and T-wave ab[illegible] normalities have usually been found. In contrast, Shibolet and associates, analyzing 36 cases of heatstroke se[illegible] Israel over an 11 year period detected electrocardiographic abnormalities other than sinus tachycardia. Patholog[illegible] changes in the myocardium in [illegible] cases have been more consistently dem[illegible] strated [1,11] but this information is of li[illegible] value in assessing the overall mode of myocardial injury in heatstroke.

In the present study myocardial da[illegible] was judged to have occurred if the [illegible] enzymes of LDH showed a pattern in[illegible] dicative of a myocardial origin. This oc[illegible] curred in 11 of 16 cases (69 per cent). The electrocardiographic changes were in the main, nonspecific and could possibly have been attributed to factors other than myo[illegible] cardial injury for example, acute elec[illegible] lyte imbalance However the frequency of abnormal ECG s (58 per cent) was [illegible] to the incidence of myocardial damage as judged by the isoenzymes. Furthermore there was a good correlation (75 per cent) between these two indices in the individ[illegible] cases. It is therefore reasonable to assu[illegible] that the electrocardiographic abnormalities reflected at least in part myocar[illegible] injury The failure to find a complete cor[illegible] relation between the two criteria does [illegible] necessarily detract from the use of eithe[illegible] as an index of myocardial damage [illegible] similar situation is encountered in a[illegible] other and more common form of myocard[illegible] injury namely myocardial infarction

Although the heart was affected in the majority of the patients, the damage w[illegible] not sufficiently severe for overt card[illegible] failure to occur This is similar to the ex[illegible] perience in other published series.[illegible] However Knochel and associates[illegible] ha[illegible] observed elevated venous pressure and pul[illegible] monary edema in patients with heatstr[illegible] which they believed were due to m[illegible] cardial damage

Serum isoenzyme changes Since m[illegible] organs are damaged by heatstroke it m[illegible] be difficult to trace the origin of the [illegible] vated serum enzymes.[illegible] This d[illegible] can be partly overcome by esti[illegible]

soenzymes. The isoenzymes of lactic de ydrogenase (LDH) have been most ex ensively studied and are of the greatest linical value at the present time. LDH is eterogenous in origin and is derived rom most tissues including heart, liver idney and skeletal muscle It can be ractionated into five isoenzymes. Wroblew ki and associates[16] and others [17] have hown that LDH 1 and to a lesser extent LDH 2 are characteristically increased in he serum in patients with myocardial in- arction In the present study the per entage of LDH 1 was found to be sig ificantly elevated in 69 per cent of he patients and it is reasonable to as- ume that this finding reflects cardiac lamage.

Electrocardiographic changes The elec rocardiographic abnormalities which have een reported in patients with heatstroke ave usually taken the form of nonspecific lattening or inversion of the T waves. [4, 5, 9] Various conduction disturbances including changing pacemaker second degree eart block, and left bundle branch lock have occurred in isolated cases. In hose patients in whom serial tracings ave been performed these changes have everted to normal in 3 to 4 months Elec rocardiographic signs compatible with myocardial infarction have been observed n 2 patients,[4,] one of whom died A pos- eroinferior infarct was demonstrated at necropsy in this patient, which the authors ttributed to heatstroke since the coronary rteries were healthy ECG's have been ecorded in a variety of experimental nimals in which hyperthermia has been rtificially induced [4-17] These have shown T wave changes atrial, nodal and ven tricular arrhythmias and varying degrees of heart block.

When interpreting electrocardiographic tracings in Bantu subjects, it is important to differentiate between those abnormalities which may be due to the disease under con- sideration and to certain changes seen in apparently normal Bantu adults. [21] Al lowing for this, a high incidence of S-T segment and T wave abnormalities was found in the present study These changes were almost invariably of mild or moderate degree and were reversible in those pa tients in whom serial tracings were per formed The changes did not fit into any definite pattern. However the same can be said for the electrocardiographic ab- normalities of myocarditis, and this does not necessarily detract from their im portance as a sign of myocardial pathology In Caucasian patients, difficulty may have been experienced in differentiating the S-T segment and T wave abnormalities from those due to underlying coronary artery disease. The fact that coronary atheroma is extremely rare in the Bantu [22,23] and virtually absent in the age group under consideration, justifies the conclusion that the abnormalities are the result of heatstroke and not due to co- existing coronary artery disease

Apart from sinus tachycardia which was invariably present for several hours after the episode of heatstroke the only arrhythmia detected was ventricular ec topic beats in a single patient. The sinus tachycardia was not thought to be of a sufficient degree to account for the S-T segment and T wave changes. Two forms of minor conduction disturbance occurred First, prolongation of the Q-T was present in 9 of the tracings and this persisted fo 2 to 10 days. Second a first degree heart block occurred in one patient and this persisted during the 5 weeks in which the patient was under observation

Pathological changes Pathological changes in fatal heatstroke have been described in some detail [11] The right side of the heart, particularly the right atrium may be dilated and this could explain the peaked P waves observed in 3 of the patients in the present study The cardiac muscle is often flabby and sub- endocardial, subpericardial, and myocardial hemorrhages are frequently found These are usually petechial but may be more extensive and commonly occur in the interventricular septum and posterior wall of the left ventricle Histological exami nation has revealed degeneration and necrosis of the muscle fibers in addition to hemorrhages Malamud and associates[1] observed such changes in one third of their patients who died within 24 hours of de- veloping heatstroke and in one half of those who survived for a longer period

These histological features were present in the 2 patients who died in the acute

stage The third patient died after 26 days and the heart was normal at necropsy All 3 had shown electrocardiographic evidence of myocardial damage shortly after developing heatstroke. LDH 1 was not elevated in the one patient in whom it was measured This discrepancy may possibly be explained by the observation in the present study that the percentage of LDH 1 may become elevated only after several days have elapsed

Pathogenesis of the cardiac lesions The cause of the myocardial damage in heatstroke is not known That direct thermal injury is at least partly responsible is suggested by the widespread nature of the tissue injury in this condition and the findings in experimental hyperthermia in animals. Another possible factor is myocardial anoxia resulting from the circulatory collapse and hypotension which are not infrequent during the acute phase Decreased coronary blood flow combined with the considerably increased oxygen demands of the tissues during the hyperpyrexial state could produce a degree of myocardial anoxia which either by itself or in association with direct thermal injury might cause cardiac damage. Finally the numerous metabolic alterations resulting from injury to other organs, such as kidney liver and brain and also the changes in electrolyte and water metabolism may all be contributory factors.

Summary

Evidence of cardiac damage was found in 17 out of 26 Bantu goldminers with heatstroke. Myocardial injury was diagnosed on the basis of serum lactic dehydrogenase (LDH) isoenzyme patterns and electrocardiographically A significant increase in the percentage of LDH 1 was present in 69 per cent of the patients. Electrocardiographic tracings were abnormal in 58 per cent of the cases The changes consisted mainly of sinus tachycardia and nonspecific S-T segment and T wave abnormalities which were reversible in those patients who were followed up A good correlation (75 per cent) was found between the isoenzyme and the electrocardiographic evidence of cardiac damage. Pathological examination of the heart in the 2 patients who died in the acute stage showed interstitial edema and degeneration of the muscle fibers Although myocardial damage occurred in the majority of the cases, in none was it severe enough to cause overt cardiac failure.

This article is published with the permission of the Chamber of Mines of South Africa. We wish to thank the Director and Deputy Director of the South African Institute for Medical Research for facilities granted. We are most grateful to Dr. J. Barlow for helpful advice and criticism and to Dr. C. H. Wyndham and the other members of the Human Sciences Laboratory for referring the patients to us. Finally we wish to thank the ... graphic Unit of the Medicine Department, University of the Witwatersrand, for reproducing the electrocardiograms.

REFERENCES

1 Leithead, C. S., and Lind, A. H. Heat stroke and heat disorders, London, 1964, Cassell & Co Ltd p. 195
2 Malamud, N. Haymaker W and Custer R P Heatstroke A clinico-pathological study of 125 fatal cases, Milit. Surg 99:397 ...
3 Kew M C Abrahams, C., Levin, N. L., Seftel, H C., Rubenstein, A. H., and Bersohn, I The effects of heatstroke on the function and structure of the kidney Quart. J Med. 36:277 1967
4. Herman R H and Sullivan, B. H J Heatstroke and jaundice, Am. J Med. 27:154, 19...
5 Allen, I V Cerebral changes in experimental heatstroke Irish J Med. Sc. 6:415, 1964
6 Metz, E. Herzschädigung durch Hitzschlag ... elektrokardiogram Klin. Wchnschr ... 1940.
7 Logue, R. B., and Hanson, J F Electrocardiographic changes following heatstroke report of a case, Ann. Int Med 21:123 1944
8 Baxter C R and Teschan, P E. ... heatstroke with hypernatremia, acute renal failure and fulminating potassium intoxication, Arch Int. Med. 101 1040, 1958.
9 Knochel J P Beisel, W R Herndon, E G. Gerard, E. S and Barry K. G. The renal, cardiovascular hematologic and serum electrolyte abnormalities of heatstroke, Am. J Med. 30:299 1961
10. Kecia, F G and Peck, O C Liver ... from heat troke Gastroenterology 43 ... 1962
11 Wilson G The cardiopathology of heatstroke J A. M A. 114:557 1940.
12 Kew M C., Bersohn, I Peter J Wyndham C H and Seftel, H. C. Preliminary observations on the serum and cerebrospinal fluid enzymes in heatstroke South Afr. M J 41:530 1967
13. Shibolet S., Coll, R ... and Sohar E. Heatstroke its clinical picture and mechanism ... 36 cases, Quart J Med. 36:525 1967
14. Wolkowskl, ... and LaDue J S ...

hydrogenase activity in blood, Proc. Soc. Exper Biol. & Med. 90:210 1955
5. Wroblewski, F Ross, C., and Gregory K. F Isoenzymes and myocardial infarction, New England J Med 263:531 1960.
6. Vesell, E. S. Significance of the heterogeneity of lactic dehydrogenase activity in human tissues, Ann. New York Acad. Sc. 94:877 1961
7. Cohen, L., Djordjevich, J and Ormiste, V Serum lactic dehydrogenase isoenzyme patterns in cardiovascular and other diseases, with particular reference to acute myocardial infarction, J Lab. & Clin. Med. 64:355, 1964
18. Grant, R. P and Estes, E. H. Spatial vector electrocardiography New York, 1951 Blakiston Division, McGraw Hill Book Company p. 55.
19 Grusin, H. Peculiarities of the Africans electrocardiogram and the changes observed in serial studies, Circulation 9:860, 1954
20. Fleischman, S J Observations on the electrocardiogram of the apparently healthy Bantu M D Thesis, U iv Witwatersrand, 1962, p. 29
21. Powell, S. J Unexplained electrocardiograms in the Bantu, Brit. Heart J 1:263 1959
22. Ferris, E. O J Blankenhorn, M A., Robinson H. W and Ceelles, G. E. Heatstroke—Clinical and chemical observations on 44 cases, J Clin. Invest. 1 :249 1938.
23. Barry M E., and King, B A. Heatstroke South Africa M J 36:455, 1962.
24. Cheer S. N The effects of high temperature on the heart and circulation in intact animals, Am. J Phys. 84:587 1928.
25. Motta, G. Il comportamento dell' lectro cardiogramma del colpo de calore provocata sul coniglio, Riv d. pat. sper 141 1937
26. Lequine, J and Danolin, H Modifications circulatoires chez le chien au cours de l'hyperthermie produits par injection intra-musculaire de 2 4 dinitrophenat de sodium, Acta brev neerl 12:3 1942.
27 Goldberg L. L, Ezell, H. K., and Walton, R. P Electrocardiographic nd serum potassium changes in fatal hyperthermia, Am. Heart J 44 754, 1952.
28. Walker A R. P Extremes of coronary artery disease mortality in ethnic groups in Johannesburg, South Africa, Editorial, Am. Heart J 66:293 1963
29 Isaacson, C., Seftel, H C Schamroth, L., and Keeley K. J Atheroma in the Bantu, Lancet 2:50, 1961

II

Serial P wave changes in acute myocardial infarction

*James I. Grossman, M.D.**
Abner J. Delman, M.D., F.A.C.P.
Bronx, N. Y.

Right atrial enlargement is frequently associated with a tall and peaked P wave of normal duration in Lead 2, 3, and/or aVF of the electrocardiogram (ECG).[3] This P wave alteration, often called P pulmonale, has been an aid in the diagnosis of acute and chronic cor pulmonale, pulmonary hypertension of other etiologies, and pulmonic stenosis. However, the P pulmonale pattern also has been recorded with left atrial pathology secondary to hypertensive heart disease, aortic stenosis, and mitral valve disease.

There have been few observations on P wave alterations in coronary artery disease. In 1933, Master[4] noted transient peaked, tall P waves, usually of normal duration, in Lead 1, 2, or 3 of the ECG in patients with acute myocardial infarction. Similar changes in P wave morphology were reported subsequently in patients with angina pectoris and acute myocardial infarction.

This paper describes P wave changes observed in serial ECG's in patients with acute myocardial infarction. The possible pathophysiologic significance of these morphologic changes will be discussed.

Materials and methods

Tall, peaked P waves occurring in Lead 2 of the ECG were noted in 30 patients with acute myocardial infarction. The clinical records of these 30 patients were reviewed. The diagnosis of acute myocardial infarction was established in each patient by history and serial electrocardiographic and serum enzyme (glutamic oxalacetic transaminase and/or lactic dehydrogenase) changes. Six patients were excluded because of concomitant chronic bronchitis and emphysema or pulmonary emboli. The remaining 24 patients had no clinical, electrocardiographic, blood chemistry, or x-ray evidence of pulmonary pathology, valvular heart disease, or congenital heart disease. The sex, age, number of previous infarctions, and the occurrence of associated diseases (such as hypertension, diabetes), congestive heart failure, shock, cardiac arrhythmias, and death were recorded in each patient. Congestive heart failure was diagnosed by clinical criteria, venous pressure and circulation time, chest x-ray, and response to digitalis and diuretics.

The serial electrocardiographic ch...

From the Cardiology Service, Medical Division, Montefiore Hospital and Medical Center, Bronx, N. Y.
Received for publication June 7, 1968.
*Cardiology Resident, Montefiore Hospital and Medical Center.
**Adjunct Attending Physician, Division of Medicine, Montefiore Hospital and Medical Center.

 March, 1969, Vol. 77, No. 3, pp. 336-

n these 24 patients were reviewed and correlated with the respective clinical course. In each patient, ECG's were obtained on the day of infarction at least every second day during the first week after the infarction and at 3 to 4 day intervals thereafter until discharge or death Three patients had ECG's taken shortly before their infarction In each instance, standard 12 lead ECG's were taken at paper speed of 25 mm per second and a sensitivity of 1 cm. per millivolt. Serial changes in the amplitude and duration of the P wave in Leads 1 2 and 3 and the terminal portion of the P wave in lead V_1, were measured with a caliper and hand magnifying lens using the methods of Goldberger[4] and Morris and associates. ECG's were also analyzed for the type and location of infarction P Ta segment changes, electrical axis, heart rate arrhythmias, and chamber hypertrophy

Results

Clinical data (*Table I*) Seventeen of the 24 patients were male. The mean age was 59 years, with 5 patients under 50 years of age, 11 patients 50 to 60 years old and 8 patients over 60 years of age. Eighteen infarctions were first episodes. Seven patients had a history of systemic hypertension. Fourteen patients developed left sided congestive heart failure during the course of their infarction (three with pulmonary edema) Three of these 14 patients also had right heart failure. Three patients two with left-sided congestive heart failure developed shock. The following transient arrhythmias were recorded in 11 patients atrial fibrillation (2) premature ventricular contractions (7) and premature atrial contractions (2)

Six patients had diabetes. Five patients died during the course of their acute myocardial infarction.

General electrocardiographic data (*Table II*) Fifteen infarctions were anterior or anterolateral, six were diaphragmatic and three were posterolateral in location. Nine patients had left axis deviation. Only two patients had abnormal P Ta segment changes Three patients had left ventricular enlargement by electrocardiographic criteria.

P wave changes (*Table II Figs 1 to 3*) Tall peaked P waves, usually of normal duration were recorded in Lead 2 in every patient during the course of myocardial

Table I Clinical data in 24 patients with abnormal P waves

	N of patients
Age (years)	
Under 50	5
50-60	11
Over 60	8
Sex	
Male	17
Female	7
Associated findings	
Prior myocardial infarction	6
Systemic hypertension	7
Left-sided congestive heart failure	14
Right-sided congestive heart failure	3
Shock	3
Arrhythmias (transient)	11
Deaths	5

Table II Electrocardiographic data in 24 patients

	N of patients
P-wave abnormalities in Lead 2	
Peaked contour	24
Maximum amplitude > 2 0 mm.	22
Maximum amplitude 2 5 mm. or more	10
Range of P wave amplitude	
Change in first 3 weeks	0 5-1 7 mm
Average P-wave change	0 87 mm.
Reversion to normal	
in 2 weeks	18
in 3 weeks	3
Remained abnormal	3
Abnormal P terminal force in Lead V_1 (> − 0 04 mm sec)	12
Location of infarction	
Anterior or anterolateral	15
Diaphragmatic or posterolateral	9

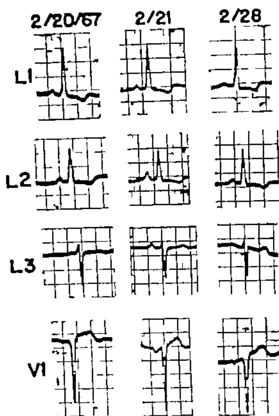


Fig *1* P tient E G w th acute terior wall myocardial infarction sustained on Feb 20 1967 Serial P w ve changes are seen most prominently in Leads 2 and V O Feb 21 tall peaked P wave of 2.5 mm. amplitude is recorded in Lead 2 nd an abormal P w ve terminal force of greater than —0 04 mm per sec. on Lead V These P w ve abnormal ties revert to normal on Feb 28 (*L1* Lead 1 *L2* Lead 2 *L3* Lead 3 *V* Lead V)

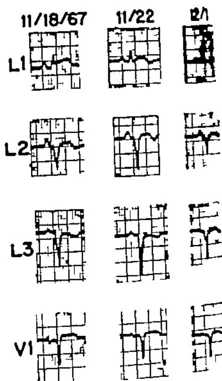


Fig *2* Patient C C ith acut anterior wall farction on Nov 18 1967 and prior diaphragmatic wall infarction. Serial P wave alterations are n Leads 1 2, and V On Nov 18 a P wave amplitude of lmost 2.5 mm is recorded Lead 2 with a concomitant borderline abnormal P wave terminal force in Lead V Normal P wave are present in the ECG of Dec. 1 (*L1* Lead 1 *L2* Lead 2 *L3* Lead 3 *V* Lead V)

infarction. The P wave abnormalities were seen on the initial ECG in 15 patients The Lead 2 P wave returned to normal size and configuration during the first week in 11 of these patients, within 3 weeks in 3 patients, and remained unchanged in one. In 9 patients, the Lead 2 P wave was normal on the initial ECG and became tall and peaked during the first week The P wave returned to normal within 2 weeks in 7 of these patients, and stayed abnormal in 2 patients. Tall peaked P waves were always present during the time of left heart failure and returned to normal as the failure improved. The maximum P wave amplitude was over 2 0 mm. in 22 patients, and 2 5 mm. or more in 10 patients. The duration was greater than 0 10 second in only 2 patients. The range of alteration of P wave amplitude was 0 5 to 1 7 mm with a mean of 0.87 mm A concomitant increase in P wave amplitude of 0 5 mm. with peaked contour was recorded in either Lead 1 or Lead in six patients.

In 12 patients an abnormal P wave terminal force of −0 04 mm. sec. or greater was recorded in Lead V₁ during the time of peaked tall P waves in Lead There were 8 episodes of congestive heart failure during this time. Six of these patients had systemic hypertension. Only of the 12 patients had neither heart failure nor hypertension

Discussion

The present study confirms previous reports of transient tall, peaked P waves

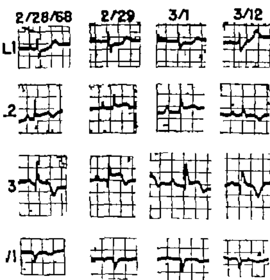


Fig. 3. Patient L. M. with acute diaphragmatic wall myocardial infarction on Feb. 28, 1968. Serial P wave changes occur primarily in Lead 2, with smaller changes noted in Lead 3. The P-wave amplitude in Lead 2 increases from 1.5 mm. on Feb. 28 to 2.5 mm. in height on Mar. 1 and reverts to normal by Mar. 12. There are no concomitant P-wave abnormalities recorded in V_1. (*L1*, Lead 1; *L2*, Lead 2; *L3*, Lead 3; V_1, Lead V_1.)

of normal duration in Lead 2 of the ECG during the course of acute myocardial infarction.[7] Peaking of the P wave in any frontal plane lead or day-to-day variation in amplitude greater than 0.3 mm. in Lead 2 is an abnormal electrocardiographic finding.[10,11] A P wave amplitude greater than 2 mm. in any of these leads occurs in less than 3 per cent of the normal population.[12] In the present series, serial alteration of the P wave amplitude greater than 0.5 mm. and a peaked contour were consistently recorded in Lead 2. The maximum amplitude was greater than 2.0 mm. in 22 of 24 patients, and was 2.5 mm. or greater in 10 patients. These variations reverted to normal in all but three patients, usually within two weeks.

The P wave changes did not appear to be related to sex, age, or the previous occurrence of myocardial infarction. They were not associated with a significantly higher incidence of shock, cardiac arrhythmias, or death compared to reported series of patients with acute myocardial infarction.[13] Master[4] also noted an absence of correlation with these clinical findings.

Four factors should be considered in the genesis of these P wave alterations: sympathetic stimulation, hypoxia, atrial infarction, and atrial hypertension and/or dilatation. Increased sympathetic activity or stimulation can increase P wave voltage. Overactivity of the sympathetic nervous system is present in congestive heart failure[14] and may also occur in the early stages of acute myocardial infarction. Hypoxia may also produce tall peaked P waves. A decrease in arterial oxygen saturation to 75 per cent can increase the P-wave amplitude and this change can be reversed by administering oxygen. Local arterial hypoxia in myocardial infarction could be secondary to low arterial oxygen saturation or to reduced blood flow related to decreased cardiac output or coronary artery vessel pathology. Atrial infarction may cause P wave changes during acute myocardial infarction. However, atrial infarction is commonly associated with P Ta segment changes or persistent atrial arrhythmias. The rarity of these findings in the present series makes atrial infarction an unlikely cause of the P wave alterations.

Thirty of the 32 patients in Master's[4] report developed circulatory failure during their acute myocardial infarction. The P wave abnormalities were greatest during the time of heart failure, and returned to normal as the failure improved. In the present study, 14 of 24 patients were in left-sided congestive heart failure, with similar serial P wave changes. Left ventricular failure is invariably associated with an elevation of left ventricular-end diastolic pressure and left atrial mean pressure. Similar pressure elevations may occur during angina pectoris, coronary insufficiency, and acute myocardial infarction without clinical signs of congestive heart failure.[15,16]

Increased posterior rotation of the P wave vector as evidenced by terminal negativity of the P wave in Lead V_1 of -0.04 mm. sec. or greater is considered a reliable indicator of left atrial overloading (hypertrophy or dilatation) and reflects any form of left-sided heart disease.[17,18] This abnormal terminal force

was present in 12 of 24 patients in the present study at the time of peaked tall P waves in Lead 2 Eight of these 12 patients were in left sided congestive heart failure at the time of the P wave abnormalities.

Thus, left atrial hypertension or dilatation may have occurred in the present series of patients during the course of their myocardial infarction with or without concomitant overt congestive heart failure In addition no patient in this study had evidence of pulmonary emboli or other pulmonary pathology and only three patients had right-sided congestive heart failure These observations suggest that the serial P wave alterations in Lead 2 may be secondary to hemodynamic changes in the left atrium although occult alterations in right atrial pressure or size cannot be completely excluded

The occurrence of the P pulmonale pattern with left atrial involvement has been reported previously Tall peaked P waves of normal duration have been observed in the frontal plane leads of the electrocardiogram in patients with left ventricular disease secondary to aortic stenosis, coronary artery disease and hypertensive heart disease P waves of normal duration and greater than normal amplitude have also been recorded in patients with mitral stenosis and proven left atrial enlargement [11,11,12] The duration of the P wave is determined primarily by the time of depolarization of the atria from the point of excitation Therefore the P wave may be of normal duration with left atrial pathology if a significant atrial conduction disturbance is not present.

This study illustrates that tall peaked P waves of normal duration may occur during the course of an acute myocardial infarction in the absence of demonstrable pulmonary emboli other pulmonary pathology or valvular heart disease Whether the serial P wave changes are primarily related to sympathetic stimulation hypoxia elevation of atrial pressure or atrial dilatation cannot be determined at the present time

Summary

Tall peaked P waves of normal duration were recorded in Lead 2 of the ECG in 4 patients during the course of acute myocardial infarction and were observed to be transient in 21 of these. No patient had evidence of valvular heart disease, pulmonary emboli or other pulmonary pathology Fourteen patients had manifestations of left-sided congestive heart failure during the time of greatest P-wave abnormality Twelve patients had concomitant abnormal posterior rotation of the P wave vector indicative of left atrial overloading The possible factors in the genesis of these P wave alterations are discussed The pattern of P pulmonale may occur during the course of an acute myocardial infarction in the absence of demonstrable pulmonary emboli or other pulmonary pathology

We would like to thank Drs. Doris J W Esk and Julius Frieden for their assistance in preparation of this manuscript

REFERENCES

1 Sodi-Pallares, D and Calder R. M: New bases of electrocardiography St Louis, 1956, The C V Mosby Company
2 Barker J M The unipolar electrocardiogram a clinical interpretation, New York, 1952, Appleton-Century-Crofts, Inc.
3 Chou T C and Helm R. A. The pseudo P pulmonale, Circulation 32:96, 1965.
4 Sano, T Hellerstein, H K and Vayda E P vector loop in health and disease as studied by the technique of electrical dissection of the vectorcardiogram (differential vectorcardiography) Am Heart J 53:854, 1957
5. Master A M P wave changes in acute coronary occlusion, Am. Heart J 8:462, 1933
6. Gross, D Electrocardiographic characteristics of P pulmonale waves of coronary origin, Am Heart J 73:453 1967
7 Bloom, N D., and Gilbert, D The atrial complex in coronary thrombosis, Am Heart J 21:602 1941
8 Goldberger E. Unipolar lead electrocardiography Philadelphia, 1949 Lea & Febiger Publishers.
9 Morris, J J Jr Estes, E. H Jr Whalen R E., Thompson H K Jr and McIntosh H D P wave analysis in valvular heart disease Circulation 29:242, 1964
10. Lepeschkin E. Modern electrocardiography Baltimore 1951 The Williams & Wilkins Company
11 Michaels, L., and Cadoret R J Day to day variability in the normal electrocardiogram Brit. Heart J 29:913, 1967
12. Lamb, Lawrence E. Electrocardiography and vectorcardiography Philadelphia, 1965, W B Saunders Company
13 Friedberg C K. Diseases of the heart, Philadelphia, 1966, W B. Saunders Company

4. Irisawa, H and Seyama, I The configuration of the P wave during mild exercise, Am Heart J 71:467 1966.
5. Chidsey C. A., Braunwald, E., and Morrow A. G Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure, Am. J Med. 39:442, 1965
6. Penneys R., and Thomas, C. B. The relationship between the arterial oxygen saturation and the cardiovascular response to induced anoxemia in normal young adults, Circulation 1:415 1950.
7. Liu C. K. Greenspan, G., and Piccirillo, R T Atrial infarction of the heart. Circulation 23:331 1961
8. Flock, D C., Valentine, P A. Treaster B Higgs, B Reid, D W Steiner R. E., and Mounsey J P D Right heart pressures in acute myocardial infarction, Brit. Heart J 29:744, 1967
9. Roughgarden, J W Circulatory changes associated with spontaneous angina pectoris, Am J M. Sc. 41:947 1966.
10. Muller O and Rorvik, K. Hemodynamic consequences of coronary heart disease with observations during anginal pain and on the effect of nitroglycerin Brit. Heart J 20:302, 1958.
21. Dimond, E G., and Benchimol, A. Correlation of intracardiac pressure and precordial movement in ischemic heart disease, Brit. Heart J 23:389 1961
22. Arevalo, A. C Spagnuolo, M and Feinstein, A. R. A simple electrocardiographic indication of left atrial enlargement, J.A.M.A. 185:358, 1963
23. Sutnick, A J and Soloff L. A Posterior rotation of the atrial vector an electrocardiographic sign of left ventricular failure, Circulation 26:913 1962.
24. Soloff L. A., and Zatuchini, J Relationship of the P wave to left atrial volume in rheumatic heart disease Am J M. Sc. 233:290, 1958.
25. Reynolds, G The electrocardiogram in mitral stenosis, Brit. Heart J 15:250 1953
26. Oliveira, J M de, and Zimmerman, H. A Auricular overloadings, Am J Cardiol. 3:453 1959

Experimental and laboratory reports

Digitalis and experimental myocardial infarction

James J Morris Jr M D
Charles V Taft M D
*Robert E Whalen M.D ****
*Henry D McIntosh M D ***
Durham N C

The question of whether acute myocardial infarction alters the amount of a digitalis-like preparation which can be tolerated without toxicity has been repeatedly raised Clinical studies and experiences, as well as animal studies, have yielded conflicting results

The present study was designed to test in the conscious, ambulatory animal tolerance to acetylstrophanthidin before during and after experimental myocardial ischemia and infarction After establishing the consistency and reproducibility of the acetylstrophanthidin tolerance test over a period of days, it was possible to serially evaluate in the same animal not only the dose necessary to produce cardiac toxicity with acetylstrophanthidin but also the duration of the toxic rhythm and the amount of drug to produce gastrointestinal intoxication. In addition, it was also possible to establish the relationship between cardiac and gastrointestinal intoxication

Method

A total of 74 farm pigs, weighing fro... to 35 pounds, were studied. Under ...thane† anesthesia an indwelling ... (volume) intravenous catheter was pl... in the superior vena cava via the ... vein in order to provide a continuous ... for intravenous injection over a ... period in the unrestrained animal. For ... each acetylstrophanthidin tolerance ... bipolar electrocardiographic leads were ap...plied to the anterior and lateral chest ... connected to a small self-contained ... telemetry unit. The electrocardiograp... signals were monitored simultaneously ... displays for immediate and delayed ... views on an oscilloscope screen, on a direct ... writing recorder and on magnetic tape for future review

The acetylstrophanthidin‡ was prepared from the powdered form and diluted to a final concentration of 0 1 mg per ml ... Quantitative chemical analyses of ...

From the Cardiovascular Laboratory Duke University Medical Center Durham, N. C.
These studies were supported by Research Grants HE-11309 He-HE-5369 and HE-07563 from the ... Institutes and Grant-in-Aid from the American Heart Association.
Presented before the fortieth annual American Heart Association meetings, October 1967 San Francisco, Ca...
Received for publication March 23 1968.

*Director Cardiovascular Laboratory Assistant Professor of Medicine, Department of Medicine, Duke ... Medical Center Durham, N. C.
**Senior Medical Student, Duke University Medical Center Durham, N. C.
***Associate Professor of Medicine Department of Medicine, Duke University Medical Center, Durham ...
****Chief, Cardiology Division, Professor of Medicine, Department of Medicine Duke University Medical ... Durham, N. C.

†Fluothane, brand of halothane furnished through the courtesy of Ayerst Laboratories, New York, N. Y.
‡Acetylstrophanthidin, in powdered form, generously supplied through the courtesy of Eli Lilly and Company ...apolis, Ind.

owed contents of 0 096 to 0 102 mg per
illiliter

The acetylstrophanthidin tolerance test
as carried out with the animal conscious
restrained and under continuous electro-
rdiographic monitoring An initial dose of
5 mg of acetylstrophanthidin was given
avenously over a 15-second period and
en followed at one-minute intervals with
10-second infusion of 0 1 mg to the point
tolerance Tolerance or toxicity was de
ed as the number of milligrams of acetyl
rophanthidin necessary to produce ven
icular or supraventricular tachycardia
hich persisted for 15 seconds Single pre
ature atrial nodal or ventricular beats,
geminal rhythm varying grades of atrio-
ntricular block or prolongation of the
R interval were not considered as end
nts. These changes did occasionally pre
ede the development of a sustained tachy
rdia, but they proved too difficult to
uantitate and recognize as reproducible
d points. The duration of the arrhythmia
d the dose necessary to produce gastro-
itestinal symptoms, vomiting or retching
ere also noted.

Acute myocardial ischemia and infarc
on were produced in the farm pig by the
ethod of Lumb and associates as modi
ed by this laboratory Under halothane
aesthesia, a left thoracotomy was per
ormed and the main branch of the left cir
umflex coronary artery was isolated dis-
ected clean and a 1 5 mm Ameroid con
rictor* placed around this vessel The
nimals recovered from this procedure and
vere conscious, eating and ambulatory
within a few hours following completion of
e surgical procedure. Sham operations
vere carried out by the same procedure as
bove except that the constrictor was re
moved after placement on the coronary
rtery

Base-line observations Each animal un
derwent 2 days of testing of acetylstrophan
thidin tolerance with notations made as to
dose in milligrams to produce toxic cardiac
arrhythmia, duration of the arrhythmia in
minutes and the gastrointestinal intoxi
cating dose in milligrams. From these obser
vations the average intoxicating dose for
each animal was determined The difference
in intoxicating dose on test day 1 and day 2
gave a measure when expressed as a
standard deviation of how much variation
could be expected in the individual tests
when performed in sequential fashion The
same type of analysis was also made on the
doses and the duration of the arrhythmia
It was hypothesized that the toxic dose, the
emetic dose and the duration of the ar
rhythmia would remain stable over the
remaining test period and that they could
be statistically predicted from the standard
deviation obtained in the 2 base-line obser
vations. After establishing the base-line
observations the animals were divided
into 3 test groups. Group I control animals
16 animals who had no further experimental
intervention after determination of the
base line values they underwent multiple
tests of acetylstrophanthidin tolerance ove
a period of several days This group would
test the theory of the stability and repro-
ducibility of the acetylstrophanthidin tol
erance test. Group II sham operated ani
mals 7 pigs underwent sham operations
and were then tested daily following this
procedure This g oup would test the in
fluence of experimental method of produc
ng myocardial ischemia and infarction but
without actual production of infarction
Group III myocardial infarction animals
8 animals underwent constrictor placement
and daily testing of acetylstrophanthidin
tolerance Each animal thus served as his
own control and the toxic dose in the con
trol group the sham group, and the myo-
cardial infarction group could be compared
on how far they deviated from their own
base-line observations.

A fourth group of 12 animals underwent
duplicate base line observations and then
were tested on the third day and repeated
0 1 mg infusion of acetylstrophanthidin
were continued after the appearance of
cardiac toxicity at one-minute intervals to
the point of ventricular fibrillation. This
group allowed a comparison of toxic and
fatal doses of acetylstrophanthidin in the
conscious ambulatory animals.

All animals in the sham and myocardial
infarction group were examined after death
to exclude infection, to determine that the
constrictor had produced a gross myocar
dial infarction in the study animals, and to

*Tierz Fennts Products, Montreal, Canada

be sure that no infarction or ischemia had been produced in the sham-operated animals.

Results

Base-line observations

CARDIAC TOXICITY A total of 43 farm pigs underwent duplicate testing of acetylstrophanthidin tolerance on 2 consecutive days. The intoxicating dose on day 1 averaged 2 20 mg of acetylstrophanthidin with a range of 1 4 to 3 5 mg On day 2 the average intoxicating dose was 2 15 mg with a range of 1 0 to 3 5 mg of acetylstrophanthidin The over-all average intoxicating dose for the 86 tests was 2 18 mg A comparison of the intoxicating dose on day 1 vs. day 2 was not statistically significant. Fig 1 shows the comparison of test day 1 and day 2 and also the individual differences in the 43 animals tested in the number of milligrams that day 2 differed from day 1 The range of differences was about ± 0 1 mg but individual tests ranged from 0 6 mg lower to 0 8 mg higher on the second day The standard deviation of the difference was 0 25 mg of acetylstrophanthidin The pattern of intoxication was similar in each animal in that the same type of arrhythmia appeared on day 1 and day 2 i.e. ventricular tachycardia preceded by premature ventricular coupling in most cases though rarely the manifestations of toxicity differed i.e. paroxysmal atrial tachycardia with varying block on day 1 versus ventricular tachycardia on day 2

DURATION OF THE ARRHYTHMIA In 38 of the animals, suitable records were available to compare the duration of the intoxication on days 1 and 2 On day 1 the arrhythmia lasted for an average of 5.7 minutes and

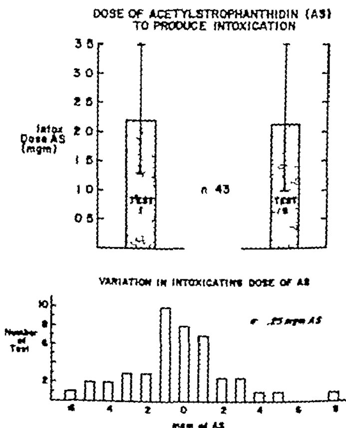


Fig 1 In the upper portion the mean intoxicating doses of acetylstrophanthidin in milligram are shown for 43 farm pigs tested on 2 consecutive days. The range of values are indicated by the bracketed line. In the lower panel the differences observed between successive tests in these 43 pigs are shown. The standard deviation calculated from this distribution was 0.25 mg

ned from 2 to 19 minutes. On day 2 the xication lasted from 2 to 19 minutes ith a higher but not significantly different ean of 7 8 minutes. The average duration t 68 tests were 6.8 minutes. The individual fferences in the duration of the intoxica on on days 1 and 2 are shown in Fig 2 he distribution was slightly skewed to a inor prolongation on day 2 The standard iation for this distribution was 4 5 nutes.

GASTROINTESTINAL INTOXICATION In 39 of he 43 animals, the dose of acetylstrophan hidin necessary to produce gastrointestinal oxication emesis or retching was ob rved on days 1 and 2. The average doses ere comparable 1 8 mg on both days astrointestinal toxicity thus generally pre ed cardiac arrhythmias for example on ay 2 G I toxicity occurred after 1 8 mg l arrhythmias after 2 15 mg In 62 of 78 sts (79 per cent) gastrointestinal toxicity d cardiac intoxication and in only 2 of the 39 animals (5 per cent) did cardiac toxicity precede gastrointestinal intoxica tion on both days 1 and 2.

Control group After performing 2 con secutive base-line tests of acetylstrophan thidin tolerance in 10 farm pigs, varying periods of time were allowed to pass before additional tolerance tests were performed Fig 3 shows a representative animal in the upper 2 panels and the results from the 10 animals in the lower panel. Two animals each were tested on the first, second and fifth days after the 2 base-line observations and 4 were tested 3 days after establishing the base-line values. Nine of 10 of these tests fell within ± 2 standard deviations (± 0 5 mg of acetylstrophanthidin) of the dose necessary to produce cardiac toxicity in the base-line observations period. The average dose for producing gastrointestinal toxicity did not differ from their 2 base-line tests, 1 9 vs. 1 95 mg The duration of the arrhythmias in the control test was 5.6

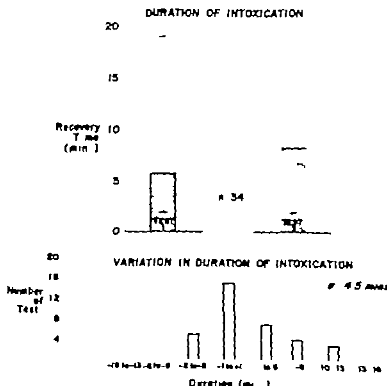


Fig. 2. In the upper portion, the mean and range of the duration of the toxic arrhythmias induced by acetylstrophanthidin in the 34 pigs are shown on 2 consecutive days. In the lower panel, the difference between the duration of the arrhythmias in minutes on the 2 consecutive days are shown on these 34 tests. Standard deviation calculated from this distribution was 4 5 minutes.

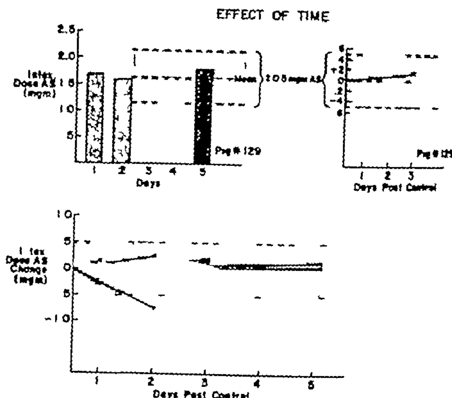
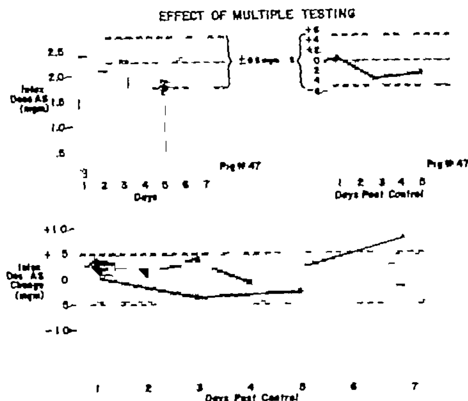


Fig 3 In the upper left are the results of the 2 base-line tests of acetylstrophanthidin in pig. The mean toxicating dose was 1.55 mg of acetylstrophanthidin. From this mean the cross hatched areas represent the projective range (± 2 standard deviations). On day five, a repeat test without further intervention showed a value of 1.7. On the right the same information is plotted using a different convention. The average base-line value is plotted at zero; 2 standard deviations are projected from this (± 0.5 mg) and the test performed on the third day was found to be 0.15 mg above the base-line average. In the lower figure the results of 10 individual animals are shown. After 2 tests, the third test was carried out with a 1 to 5 day interval. Note that 9 of the 10 tests fall within ± 2 standard deviations.

minutes as compared to their base-line value of 5.7 minutes.

After performing 2 consecutive base-line tests of acetylstrophanthidin tolerance in 6 farm pigs, multiple tests were carried out over a period of several days to test the stability of the test. Fig 4 shows a representative animal in the 2 upper panels and the results in the 6 animals below. The individual animals underwent from 2 to 5 tests after the base line tests. In the 6 animals a total of 20 tests of acetylstrophanthidin tolerance were carried out over a 7-day period. Of the 20 tests, 19 fell within ± 2 standard deviations of the value obtained during their base-line observations. In one test on the seventh day the tolerance rose by 0.8 mg. The duration of the intoxication in these 20 tests was exactly equal to their base line duration 5.7 minutes. The dose to produce gastrointestinal symptoms was 2.0 mg and did not differ from the base-line value of 1.8 mg. In F per cent of the control tests, gastrointestinal toxicity preceded the cardiac arrhythmia, similar to the 79 per cent figure mentioned above in the base-line values.

In summary the 16 farm pigs where base line observations were carried out and then a total of 30 tests performed over a one-week period after varying periods of delay and with multiple testing 28 of the 30 tests fell within ± 2 standard deviations of the dose of acetylstrophanthidin necessary to produce intoxication in the base-line test period. One test fell by more than standard deviations and one rose by more than this amount. In these 30 tests in 16 pigs, the average intoxicating dose was 2 mg compared to 2.18 mg for the 86 te



. 4 The same con entions are used that were used n Fig 3. O the upper left, single pig had 2 base-line sts performed, the average of these tests are projected and ± 2 tandard deviations are cross hatched. Three sts ere then performed without further i tervention all fell with the projectn range On the right, iations from the projected mean intoxicating dose are show n for this same nimal I the lower portion the results from 6 animals where m ltiple tests were carried out over 7-da period. All fell w thin the dicted range.

rformed in the base-line tests in 43 pigs. he duration of the arrhythmias was 5 7 minutes in the 30 tests vs. 6 8 minutes in he 63 base line tests. Gastrointestinal in oxication occurred at 1 95 mg over the ats from the third to the seventh day compared to 1 8 mg in the base-line ests. All of these differences were not tatistically significant and suggest that ime or multiple testing does not alter cetylstrophanthidin tolerance. Thus the tial hypothesis of a stable and pre dictable pattern to acetylstrophanthidin ntoxication in the conscious animal was atisfied.

Sham operations Seven farm pigs, after se-line observations of acetylstrophan thidin tolerance underwent a sham opera tion and then were tested for acetyl strophanthidin tolerance over the next 3- to 10-day period Pathologic examination of these animals at the end of that time showed minor areas of focal pericarditis about the dissected area of the left circum flex coronary artery but in each case the vessel was patent and no evidence of myo-cardial infarction was found. Fig 5 shows a representative animal in the upper 2 panels and the results of all the tests in the lower panel A total of 34 tests were carried out during the postsham period 31 of these tests (94 per cent) fell within ± 2 standard deviations of the value for the dosage of acetylstrophanthid n re quired in the presham period to produce intoxication. In the lower half of Fig. 5 it can be seen that of the 3 tests falling outside the predicted range, 2 fell by 0 7 and 1 0 mg on the first day and in one animal the dose increased by 0.65 mg on the second day after the sham procedure. The average intoxicating dose in the 34 tests in the 7

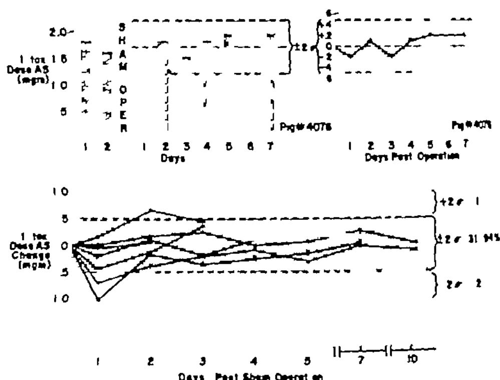


Fig 5 The res lts of a sham operation are shown in the single pig in the pper 2 panel and the results ... mal the lower portion The sham operation was performed immediately after the second base ... nd daily testing carried out the next 5 day nd in some cases 10 day post ham operation. Thirty ... the 36 tests were found to fall within ± 2 tandard deviation of their base-line tests. T o tests ... test fell outside these limit

pigs was 2.0 mg and the average for the 14 tests in the duplicate base-line tests in these 7 pigs was 1.9 mg

The duration of the arrhythmias in the sham-operated group of animals averaged 7.4 minutes with a range of 2 to 19 minutes. The 14 base line tests in this group had an average duration of intoxication of 7.5 minutes with a range of 2 to 19 minutes. All fell within ± 2 standard deviations of their base line observations

Gastrointestinal intoxication occurred prior to cardiac arrhythmias in 24 of the 32 tests in the sham period (73 per cent) and the average dose to produce these gastrointestinal symptoms was 1.8 mg of acetylstrophanthidin. In the 14 base-line tests in the 7 sham animals 12 had gastrointestinal intoxication prior to cardiac arrhythmias (86 per cent) and the average dose was 1.7 mg. In summary in the animals who underwent sham procedures 34 acetylstrophanthidin tolerance tests were performed over a period of 7 days, and change in the intoxicating dose the duration of the arrhythmias or the relation of cardiac and gastrointestinal intoxication were noted. The electrocardiographic pattern of intoxication was not changed from the control observations.

Myocardial infarction Eight animals underwent duplicate base-line tests and acetylstrophanthidin tolerance and then were subjected to placement of an ... constrictor on the left circumflex coronary artery. Following this, tests were carried out for periods up to 10 days after constrictor placement. At postmortem examination in each of these animals except 2 who died at approximately 36 hours evidence of posterior and posterolateral infarctions were found. These varied from small subendocardial scars approximately 1 cm in size to large full thickness ...

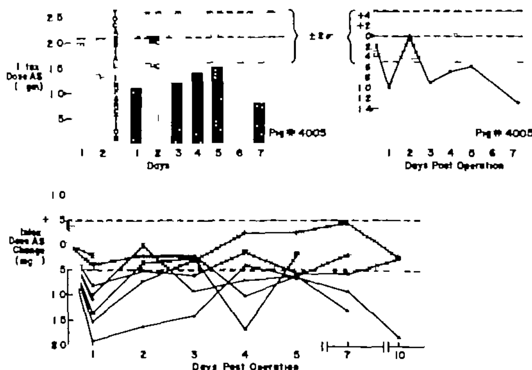


Fig. 6 The results of experimental infarction are shown single animal in the upper panels and all 8 animals studied in the lower portion. In the upper portion, tests performed on days 1 3 4, 5 and 7 after surgical placement of an Ameroid constrictor fell by 0.6 mg to as much as 1 3 mg Only one test, day 2, fell within the predicted range. In the lower portion, remarkable portion of tests falling outside predicted range are evident

...uring several centimeters in size. In the early deaths, microscopic studies showed early changes of tissue necrosis in the posterior coronary circulation In each case the Ameroid constrictor was found to have the vessel completely occluded

In the 40 tests performed over a 10-day period after placement of an Ameroid constrictor on the left circumflex coronary artery the average intoxicating dose fell to .5 mg of acetylstrophanthidin. In the 16 base-line tolerance tests in these animals prior to myocardial infarction the intoxicating dose averaged 2.2 mg thus this represented a fall of 32 per cent Fig 6 shows the individual values for the 8 animals. Twenty two of the 40 tests performed (55 per cent) fell by more than 2 standard deviations below their base line values of acetylstrophanthidin tolerance. Inspection of Fig. 6 reveals that a significant fall in the amount of acetylstrophanthidin to produce arrhythmias was a finding in 7 of the 8 pigs tested The only animal who failed to show this was animal No 38 who died spontaneously 36 hours after constrictor placement and who had only one tolerance test performed after surgery The changes in tolerance were sporadic in that certain animals showed wide variations from day to day a phenomenon not observed in the control or sham group (see Figs. 4 and 5) No relationship was discernible between the extent of the pathologic changes observed and the magnitude of the fall in acetylstrophanthidin tolerance. Although no consistent pattern of change was evident in acetylstrophanthidin tolerance after infarction 4 of them (Nos. 12 4005 33 and 89) showed a reduction in the threshold in the first few days and then returned to almost normal tolerance and displayed a second fall on the fourth or fifth day

The duration of intoxication was pro-

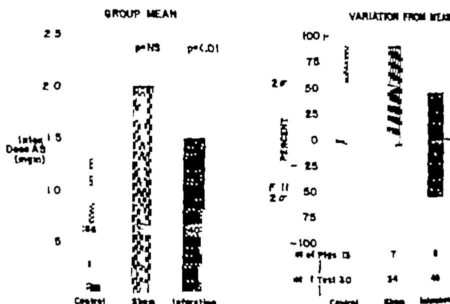
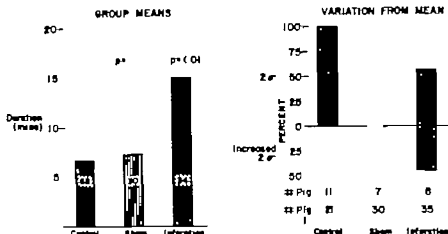


Fig 7 On the left are the average intoxicating doses in the control sham-operated group and those with infarction The P values are compared to the control group and the number of tests performed are below in their respective bars On the right the per cent of tests falling within 2 standard deviations above zero and the per cent of tests falling by 2 standard deviations or more are shown below zero. The number of pigs tested and the total number of tests in each group are shown below the respective bars. Controls are those situations where no intervention was carried out except repeated testing

longed by the production of experimental infarction The average duration of the intoxication in the 34 tests observed after constrictor placement was 15 minutes as compared to an average of 7 4 minutes in the 16 base-line tests for these animals. In 15 of these 40 tests (38 per cent) the arrhythmia lasted longer than 20 minutes a duration observed only once in the 86 base-line tests the 30 tests over multiple days in the control group and the 34 tests in the sham group (1 in 150 tests, 0 7 per cent)

Gastrointestinal intoxication was rarely noted in the tests performed in the post infarction period Of 33 tests performed where the relationship of cardiac and gastrointestinal intoxication were noted in only 5 instances did gastrointestinal intoxication precede arrhythmias (14 per cent) In the 5 instances where gastrointestinal intoxication occurred first the average dose was 1.8 mg which was unchanged from the base-line values. The threshold for developing gastrointestinal intoxication was not changed but since the average intoxicating value was lowered by experimental infarction cardiac toxicity was reached before gastrointestinal symptoms occurred

Comparison of control sham and infarction animals The doses of acetylstrophanthidin necessary to produce sustained cardiac arrhythmias in base-line tests for animals the sham-operated animals and the animals who experience myocardial infarction are shown on the left of Fig 7 and their respective values were 2.1, and 1 5 mg of acetylstrophanthidin. Statistical testing of these 3 group means showed that the myocardial infarct group differed from the controls significantly ($p < 0.01$) On the right side of Fig 7 where each animal is used as his own control the per cent of tests which differ by more than 2 standard deviations from the base-line test values are shown. The control group are made up of those tests performed in 16 pigs after 2 base-line tests were performed and then subsequently tested after varying periods of time



8. The duration of the intoxicating dose for the 3 groups are shown. On the left, the group mean and num of tests are compared. On the right are deviations from base line tests. The duration was doubled and nly 50 per cent of the animals had prolongation of the toxication beyond 2 standard deviations after perimental infarction.

rther intervention. In the control sham d myocardial infarction groups 3 6 and per cent fell 2 standard deviations (0 5 g. of acetylstrophanthidin or more) below eir base-line values. Further statistical sting of the same 3 populations, for their riance in milligrams of acetylstrophan ndin from their base-line values, showed at the control and sham groups did not ffer from their base-line values, but that e infarction group varied significantly om their base-line values ($p < 0.01$). The ll in milligrams of acetylstrophanthidin fter infarction varied from 0 1 mg to as uch as 1 8 mg and the average fall from eir own base-line mean values was 32 per ent, 2.2 to 1.5 mg.

The duration of the arrhythmias in the ase-line tests, the sham and infarction nimal are shown in Fig 8. On the left are he group averages, the infarction group howed a doubling of the duration of the rrhythmia, significantly different from the ase-line and sham groups ($p < 0.01$). On he right of Fig. 8 are shown the per cent of nimals who had prolongation of the ar hythmia by more than 2 standard devia ions above their own base-line values greater than 9 minutes longer than con rols). In 21 control tests in animals with ut further intervention except repeated testing after their base-line values all fell within ± 2 standard deviations. In the sham group only 9 per cent lasted longer than standard deviations above their base-line duration while 45 per cent of the tests in the myocardial infarction group exceeded their base-line values by at least 2 standard deviations. No test in the con trol or sham groups had a duration of the arrhythmia longer than 19 minutes whereas many tests in the infarction group lasted longer than 30 minutes.

The doses of acetylstrophanthidin neces sary to produce gastrointestinal intoxica tion in the 3 groups are shown in Fig 9 on the left. No significant variation is seen in the 3 groups however the number of ani mals in the myocardial infarction group is extremely small. The reason for this differ ence is shown on the right of Fig 9. Gastro- intestinal toxicity preceded cardiac arrhyth mias in 79 per cent of the base-line and in 70 per cent of the sham group while this occurred in only 14 per cent of the myo- cardial infarction group. Thus, only 5 animals were available to calculate the gastrointestinal intoxicating dose since in the remaining 84 per cent of the animals the test was halted because of the appearance of cardiac toxicity before gastrointestinal intoxication appeared.

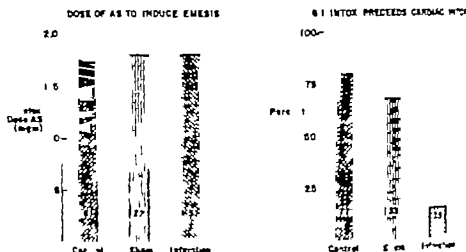


Fig 9 Th dose of cet lstrophanthidin t produce gastrol testinal intoxication is shown on the left A the erage alues ere identical, note that onl 5 observations were obtainable in the infarction group the right are th pe ce t of mals where gastrointestinal intoxication preceded arrhythmias In the and sham-operated mals this was the usual sequence In the animals after infarction, only 13 per of the test were observed where GI symptoms were noted before arrhythmias occur thus the small observ tion v lat le on the left portion of the figure

Mortality and relationship of toxic and lethal doses The performance of the acetyl strophanthidin tolerance test, as defined by requiring the production of a sustained arrh thmia for at least 15 seconds, produced fatal ventricular fibrillation in approximately one out of every 20 healthy farm pigs tested Repeated daily testing did not increase this mortality rate In the 7 animals who underwent 34 tests after a sham operation 2 animals died of ventricular fibrillation induced in the course of testing In the 8 animals who had surgical placement of an Ameroid constrictor on the left circumflex coronary artery animals died of acetylstrophanthidin induced ventricular fibrillation in the course of performing 40 tolerance tests Animal Nos. 17 and 4005 died on the fifth and seventh days postsurgery at the time of testing. Two animals died spontaneously approximately 36 hours after constrictor placement presumably of a fatal arrhythmia induced in the process of gradual coronary constrictor closure Both animals had recovered several hours earlier from their first acetylstrophanthidin tolerance test performed in the first 24 hours following surgery Thus alth cardiac arrhythmias were induced at lower dosage and lasted for a longer per of time no difference in the mortality was noted in the performance of ace strophanthidin tolerance tests in the c trol sham or myocardial infarction gr of animals.

In 12 additional animals duplicate b line observations of the arrhythmia p ducing dose were found to 2.20 mg w range of 1.20 to 2 60 mg On the third d the test was repeated but then cont past the toxic arrhythmia to the p fatal ventricular fibrillation. The fatal d averaged 2 84 mg of acetylstrophan with a range of 1 90 to 3.30 mg Thus lethal dose exceeded the toxic dose b mg with individual difference of 0 1 10 mg The average toxic dose sented 77 per cent of the lethal dose range of 61 to 88 per cent in the animals.

Discussion

Acetylstrophanthidin because of its onset and its rapid d ssipation of act

m used to assess the level of digitalization. Because of the fatal complications encountered in this test, however, it has been abandoned for clinical use. Nevertheless, these previous uses in humans have suggested that it is additive to other cardiac glycosides, i.e., digitoxin, digoxin, and that the amount which can be given without producing intoxication is dependent on the amount of these other digitalis-like drugs present. It seems justifiable then to assume that tolerance to acetylstrophanthidin probably parallels tolerance to other cardiac glycosides closely. Because of this speed of action and since it behaves as if it is additive and similar to other glycosides, we have chosen this agent as a drug for testing digitalis tolerance under our experimental conditions. Furthermore, acetylstrophanthidin can be prepared in a very purified form and, thus, can be administered in very precise and reproducible amounts.

The farm pig was chosen for this study because of the characteristics of its coronary circulation; the distribution of the major coronary vessels parallels that found in man. In this animal the experimental technique for the production of a gross myocardial infarction has been well outlined. The hydroscopic nature of the Ameroid material in the constrictor produces gradual occlusion of the coronary artery with subsequent necrosis of the myocardium when the animal has recovered from surgery and is conscious and ambulatory. A constrictor of 1.5 mm. was chosen to provide for sufficient closure to produce ischemic electrocardiographic changes in 12 to 18 hours and histologic evidence of tissue necrosis in 24 to 48 hours. The left circumflex coronary artery was chosen to avoid the high mortality rate associated with constrictor placement on the anterior descending coronary artery and also to allow for testing of acetylstrophanthidin tolerance without ventricular arrhythmias, which are uniformly present in the first few days after anterior descending coronary occlusion. These studies do not apply to right coronary artery occlusions, where the problem of varying grades of atrial and atrioventricular block are added to myocardial necrosis.

By using indwelling intravenous catheters, continuous telemetry of the electrocardiogram, the production of experimental myocardial infarctions by the use of an Ameroid constrictor and by the use of acetylstrophanthidin repeated daily tests of digitalis tolerance could be performed in a conscious, unrestrained ambulatory animal before, during, and after the gradual occlusions of a major coronary artery which results in a histologic and gross myocardial infarction.

The amount of acetylstrophanthidin in milligrams in the conscious, unrestrained animal proved to be a reproducible and reliable measure for producing sustained arrhythmias. The duration of the arrhythmia and the appearance of gastrointestinal intoxication also was reproducible and predictable. In 43 farm pigs duplicate testing to the point of cardiac arrhythmias showed that the tests were reproducible with a standard deviation of 0.25 mg. of acetylstrophanthidin and the duration of the intoxication was reproducible with a standard deviation of 4.5 minutes. After establishing these limits, it was possible to demonstrate that after duplicate base-line *determination of the arrhythmia producing* dose and noting the emetic dose and the duration of the arrhythmia, multiple tests and tests over a 7-day period could be performed and they would fall within the limits of 2 standard deviations of the base-line values with an accuracy of 95 per cent. This observation then verifies the stability and reproducibility of the tests in a farm pig subjected to no experimental manipulations. This test should provide a valuable tool for studying various pharmacologic, environmental, and physiologic interventions on acetylstrophanthidin tolerance.

The validity and reproducibility of the test was further substantiated by the 34 tests performed after the sham operation in 7 animals. In addition, these data suggest that the performance of a thoracotomy, the focal areas of pericarditis produced, and the obvious changes in electrolyte balance which must ensure in the first few days postoperatively all fail to produce detectable changes in the tolerance of these animals to acetylstrophanthidin. In these animals, the dose to produce cardiac arrhythmias, their duration, the emetic dose, and the relationship between cardiac and gas-

trointestinal intoxication were unchanged from control observations

In those animals who underwent experimental myocardial infarction striking changes occurred in the tolerance to acetylstrophanthidin The average dose to produce intoxication was reduced by approximately 1 3 the arrhythmias lasted twice as long and the normal pattern of gastrointestinal intoxication preceding cardiac arrhythmias was reversed so that in most animals (85 per cent) the cardiac arrhythmia was the first sign of intoxication Lowering of the requirements of acetylstrophanthidin to produce the arrhythmia and the failure of the gastrointestinal threshold to fall and the marked prolongation of the duration of the arrhythmia suggest that these changes were not nonspecific changes due to the operative trauma but were in some ways specifically affected by the production of ischemia and myocardial infarction The sham operated animals further attest to this explanation

Certain features were worthy of comment by their absence No changes in the type of arrhythmia produced by the drug were evident and although the arrhythmias were considerably longer there were no discernible changes in the mortality rate in the myocardial infarction group due to the testing itself Obviously if the same dose were administered in these animals during the course of myocardial infarction as they previously tolerated in the base-line period the mortality rate would have been greater but the tests were all terminated at the appearance of a sustained arrhythmia.

The magnitude of these changes was striking in their absolute value in some of the animals a 50 to 60 per cent reduction in the intoxicating dose was demonstrated No uniform pattern was observed except that a general reduction in dosage was evident with occasional sharp rises and falls in tolerance during the 7 to 10 days after infarction. Further testing for prolonged periods of time have not been carried out to assess acetylstrophanthidin tolerance in the face of a healed myocardial infarction

The reasons for these changes in tolerance are not apparent from these studies. As mentioned above one can reasonably well exclude those factors outside the specific production of myocardial damage due to lack of change in the sham group [illegible] acetylstrophanthidin produced a [illegible] physiologic intoxication in the [illegible] cells at a much lower concentra[illegible] whether the drug is abnormally [illegible] trated in these damaged cells [illegible] It appears sufficient to say that in the animals with experimental myocardial infarction rapid intravenous administ[illegible] of acetylstrophanthidin and probably [illegible] digitalis-like drugs is fraught with [illegible] erable danger and one would be advi[illegible] proceed with caution and use smaller [illegible] than generally predicted from the [illegible] or normal values.

These studies tend to confirm the [illegible] experimental animal work where approxi[illegible] mately a 25 per cent reduction in [illegible] dosage was noted after acute myocardial infarction.[3,4] These data also [illegible] that certain clinical instances of [illegible] sensitivity to digitalis preparations [illegible] myocardial infarction may present a [illegible] and analogous situation.[11]

Summary

Acetylstrophanthidin tolerance te[illegible] carried out in a series of farm pigs [illegible] conscious unrestrained state. Serial te[illegible] of these animals showed that the dose [illegible] produce cardiac arrhythmias, the dur[illegible] of the arrhythmias, and the gastrointes[illegible] toxic dose were predictable and [illegible] measures.

Three groups of animals were compar[illegible] a control group a sham operated gr[illegible] and a group who experienced gradual [illegible] cumflex coronary occlusion and subse[illegible] infarction. The experimental infarction [illegible] induced by an Ameroid constrictor [illegible] this technique it was possible to carry [illegible] serial observations of acetylstrophanth[illegible] tolerance during the evolution of the [illegible] farction

The toxic dose the duration and [illegible] arrhythmias, and the gastrointestinal [illegible] icating dose remained unchanged in the [illegible] control and sham groups. In the [illegible] studied during the evolution of exp[illegible] mental myocardial infarction the [illegible] intoxicating dose was reduced by appro[illegible] mately 1/3 the arrhythmias lasted [illegible] as long and the usual pattern of ca[illegible] intoxication preceding GI symptoms [illegible] reversed

REFERENCES

Gold H. Action of digitalis in the presence of coronary obstruction. An experimental study Arch. I t. Med. 35:482, 1925.

Bellet, S Johnston, C. G and Schecter A. Effect of cardiac infarction on the tolerance of dogs t digitalis Experimental study Arch. I t Med. 54:509 1934

Travell, J Gold, H and Modell, W Effect of experimental cardiac infarction on response to digitalis, Arch. Int Med. 61 184 1938.

Askey J M Digitalis in acute myocardial in farction, J.A.M.A. 146 1008, 1951

Boyer, N H Digitalis in acute myocardial infarction New England J Med 252:536 1955

Hood, W B., J McCarthy B and Lown, B Hemodynamic effects of isoproterenol and acetylstrophanthidin in acute myocardial infarction in dogs, Circulation Res. 21 191 1967

7 Friedberg, C. K. Diseases of the heart Philadelphia, 1966, W B. Saunders Company

8 Lumb G Singletary H. P and Hardy L. B Collateral circulation in the heart, Angiology 13:463, 1962.

9 Hurst, V W III Morris, J J J Zeft, H. J Hackel, D B., and M Intosh, H D Increased survival with prophylactic quinidine after experimental myocardial infarction, Circulation 36:294 1967

10 Lown, B and Levine S. A C rrent concepts in digitalis therapy Boston, 1954 Little Brown & Company

11 Lown, B., Vassaux, C Hood, W B., J Fakhro, A M Kaphaahy E and Roberge, G Unresolved problems in coronary care, Am J Cardiol. 20:495 1967

Right coronary blood flow in acute pulmonary embolism

*Paul D. Stein, M.D.**
Shukuel Al Kabbkoun, M.D.
Hubert F. Hawkins, M.D.
John W. Hyland, M.D.
Charles E. Jarrett, M.D.
Dallas, Texas

Myocardial ischemia, as shown by electrocardiographic changes [1-4] and autopsy studies, [2,4] is frequently seen after acute pulmonary embolism. Ischemic myocardial damage has been shown in some patients who have died of pulmonary embolism even though the coronary arteries were normal. [2,3] The cause of myocardial ischemia after pulmonary embolism is not entirely clear. Hypoxemia, pulmonocoronary reflex spasm, shock, and right ventricular strain have been suggested as possible causes. [2] In a previous study by some of us it was shown that left circumflex coronary blood flow, in the absence of shock, increased after acute experimental pulmonary embolism. [5] No support was found for the concept of pulmonocoronary reflex spasm. The purpose of this study is to determine the effect of acute experimental pulmonary embolization on blood flow in the *right* coronary artery. Measurement of right coronary arterial blood flow during acute pulmonary embolism will determine if the myocardial ischemia under these circumstances is related to diminished right coronary blood flow caused by spasm of the right coronary artery or pressure changes within the right ventricle.

Material and methods

Acute pulmonary embolism was produced in eight open-chest anesthetized healthy pigs weighing 30 to 42 kilograms. Chloralose anesthesia administered intravenously in a dose of 80 mg. per kilogram of body weight was utilized because the drug does not appear to interfere with the autonomic nervous system.[6] Respiration was maintained by a Harvard pump after insertion of a cuffed tube through a tracheostomy. A mixture of air and oxygen was administered to all animals after the chest was opened to insure a normal arterial oxygen saturation before pulmonary embolization. Neither the amount of oxygen administered nor the rate of

From the Department of Medicine, Baylor University Medical Center, Dallas, Texas.
This work was supported in part by the Dallas Heart Association and the National Institutes of Health, U. S. Public Health Service, Grant No. HE8511-0.
Received for publication April 1, 1968.
*Address for reprints and proofs: Paul D. Stein, M.D., Creighton University Cardiac Center, 2305 ... Neb. 68...

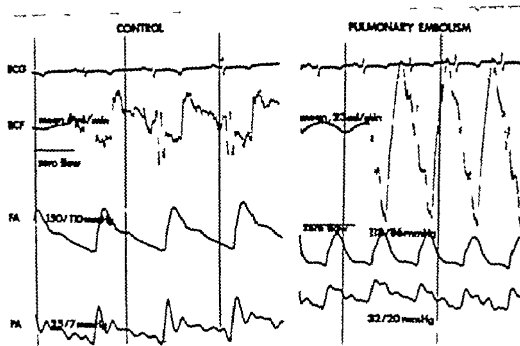


Fig. 1. Fig 3. Right coronary flow (*RCF*), femoral arterial pressure (*FA*), pulmonary arterial pressure (*PA*), and electrocardiogram (*ECG*) before and after pulmonary embolism. Both mean and pulsatile *RCF* are shown. Zero flow baselines, as indicated by mechanical occlusion, have been added. Time lines are at 1 sec. intervals. Mean *RCF* increased from 6 to 23 ml. per minute following pulmonary embolization in quantities sufficient to increase *PA* from 25/7 to 32/20 mm. Hg. The *FA* decreased from 150/110 to 118/86 mm. Hg. The *ECG* did not change.

respiration was changed after control measurements were made unless otherwise specifically stated.

Electrocardiograms were taken and blood flow in the right coronary artery, pressures in the pulmonary artery, right atrium, and femoral artery, cardiac output, and arterial blood pH, partial pressure of oxygen, and partial pressure of carbon dioxide were measured before and intermittently for 2 to 15 minutes after pulmonary embolization. Pulmonary embolization and recordings were repeated until mean pressure in the pulmonary artery was above 30 mm. Hg. Following pulmonary embolization, the effect of the improvement of arterial oxygenation by breathing increased amounts of oxygen was observed.

Pulmonary embolization was induced by injection into the jugular vein of fresh autologous blood clots produced in vitro. Postmortem dissections showed that emboli dispersed widely throughout the pulmonary vasculature. Right coronary arterial blood flow was measured by means of a BL-410 electromagnetic flowmeter* with a 1.5 or 2.0 mm. diameter (BL-1015 or BL-1020) flow transducer placed around the surgically exposed vessel. Zero flow was indicated by mechanical occlusion of the artery by means of a snare placed 1 or 2 mm. distally to the flow transducer. There were no coronary arterial branches between the snare and the flow transducer. Flow transducers were calibrated by placing them about sections of excised vessels and running saline through them with timed collections. Calibrations with saline reportedly do not differ by more than 7 per cent from calibrations with blood.

Pressures were measured by appropri

*Biotronex Laboratory, Inc., Silver Spring, Md.

ately positioned catheters attached to Statham P23db strain gauge transducers. Recordings were made on an Electronics for Medicine 8 channel recorder Cardiac output was measured by the indicator dilution technique with the use of indocyanine green A 6 lead electrocardiogram was taken before exposure of the right coronary artery and before and after pulmonary embolization The position of the pig was kept constant throughout the study in order to avoid postural variations in the electrocardiogram Precordial leads were omitted because the chest was open throughout the experiment Measurements of arterial blood pH partial pressure oxygen and partial pressure of carbon dioxide were made in duplicate on a Micro pH and Blood Gas Analyzing System† Arterial oxygen saturation was measured by means of an Oximeter.‡

Right coronary resistance (RCR) was calculated as the ratio of femoral arterial mean pressure (in millimeters of mercury) to right coronary mean flow (in milliliters per minute) and recorded in dyne-sec cm⁻⁵ by multiplying this ratio by the conversion factor 79.92×10^3 Total pulmonary resistance and work of the right ventricle were calculated as described by Dexter and associates.

Results

Initial pulmonary embolizations increased the average pulmonary arterial mean pressure from 1? to 24 mm Hg Subsequent embolizations increased the pulmonary arterial mean pressure to an average of 42 mm Hg Average right coronary mean flow increased 38 per cent following initial embolizations and doubled after subsequent embolizations (Figs. 1 and 2) Cardiac output and heart rate showed little change and femoral arterial mean pressure increased somewhat Hypoxemia occurred in most pigs following repeated pulmonary embolizations.

Emphasis in this study was placed on the observation of right coronary blood flow before the onset of shock. As would be expected blood pressure and cardiac output decreased in all animals prior to death. It was not the purpose of this in

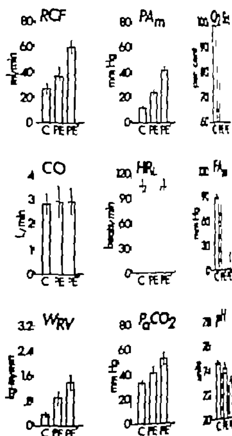


Fig 2 *A* Effect of pulmonary embolism on right coronary mean flow (*RCF*), pulmonary arterial mean pressure (PA_m), and arterial oxygen saturation (O_2Sat). Control (*C*) levels and levels after initial pulmonary embolization (*PE*) and repeated pulmonary embolizations (*PE'*) are shown. The standard error of the mean (±) is indicated by vertical lines at the top of each bar graph. Average RCF increased from 27 to 37 ml./min. following initial pulmonary embolizations (P < 0.05) and increased to 61 ml./min. following repeated embolizations (P < 0.001). Average PA increased from 1[illegible] to 24 mm. Hg after initial embolizations (P < [illegible]) and increased to 42 mm. Hg after repeated embolizations (P < 0.001). Average arterial oxygen saturation remained normal after initial pulmonary embolizations and decreased to 79 per cent after repeated embolizations (P < 0.01).

B Effect of pulmonary embolism on cardiac output (*CO*) heart rate (*HR*), and femoral arterial mean pressure (*FA*). Neither *CO* nor *HR* showed significant changes. Average *FA* increased from control level of 88 mm Hg to 105 mm. Hg after repeated pulmonary embolizations (P < [illegible]).

C, Effect of pulmonary embolism on right ventricular work (W_{RV}) partial pressure of carbon dioxide in arterial blood (P_aCO_2), and arterial blood pH (*pH*). Average W_{RV} increased from [illegible] to 0.90 kg M per min following initial embolizations (P < 0.01) and increased to 1.4 Kg-M per min following repeated embolizations (P < 0.001). Following initial embolizations the average P_aCO_2 increased from 33 to 41 mm. Hg (P < [illegible]) and average pH decreased from 7.46 to 7.41 (P < 0.02) After repeated embolizations average P_aCO_2 increased to 53 mm. Hg (P < [illegible]) and average pH decreased to 7.31 (P < [illegible]).

---

*Statham Instruments, Inc., Los Angeles, Calif.
†Instrumentation Laboratory, Inc., Watertown, Mass.
‡American Optical Company, Buffalo, N. Y.

stigation to study coronary blood flow ring that time.

The average right coronary mean flow reased 38 per cent from a control flow 27 ml. per minute to 37 ml per minute the six pigs that sustained an initial bolization that raised the mean pul nary arterial pressure to an average 24 mm. Hg ($P < 0.05$) Four pigs owed an increased right coronary mean w and two pigs showed no change. verage right coronary mean flow in ...d 120 per cent to an average of 61 l. per minute following subsequent em lizations that raised the mean pulmonary terial pressure to an average of 42 mm. ($P < 0.001$) (Fig 2) Each of the eight gs showed an increased right coronary w after repeated embolizations.

The resistance in the right coronary terial bed decreased from an average 390×10^3 dyne-sec.-cm.$^{-5}$ to 220×10^3 ne-sec.-cm.$^{-5}$ following initial emboliza ons and decreased to 150×10^3 dyne-sec m.$^{-5}$ following repeated pulmonary em lizations. The diminished right coronary sistance observed after pulmonary em lization was not statistically significant.†

The total pulmonary resistance increased om an average control value of 370 ne-sec.-cm.$^{-5}$ to an average of 1 300 yne-sec.-cm.$^{-5}$ after repeated pulmonary mbolizations ($P < 0.01$) Right ventricu r work increased from an average control ue of 0.36 Kg M per minute to an erage of 1.4 Kg M per minute after peated embolizations ($P < 0.001$) (Fig) Both pulmonary resistance and right entricular work increased in smaller mounts after initial pulmonary emboli ions.

The average cardiac output and heart ate remained essentially constant during he intervals described in this study al changes in individual pigs were riable The average femoral arterial mean pressure increased from a control of 88 mm. Hg to 105 mm. Hg after re peated embolizations (Fig 2)

The arterial oxygen saturation was normal in all pigs before pulmonary em bolization and remained normal after initial embolizations. The arterial oxygen saturation decreased to an average of 79 per cent (range 61 to 90 per cent) following repeated pulmonary embolizations ($P < 0.01$) (Fig) The average partial pressure of oxygen in arterial blood was 171 mm. Hg before pulmonary embolization, 97 mm. Hg after initial pulmonary emboliza tions, and 53 mm. Hg (range 31 to 76 mm Hg) after subsequent pulmonary emboliza tions ($P < 0.001$)

The average arterial blood pH was 7 46 units before pulmonary embolization The arterial blood pH decreased or remained constant in all pigs after pulmonary em bolization. The average decrease was 0.05 unit after initial embolizations ($P < 0.02$) and 0 14 unit after subsequent embolizations ($P < 0.01$) The partial pressure of carbon dioxide in arterial blood increased from an average control value of 33 mm Hg to 41 mm. Hg after initial embolizations ($P < 0.05$) and increased to an average of 53 mm Hg after subse-quent embolizations ($P < 0.001$) (Fig 2)

Depression of the *ST* segments or inver sion of the T waves in the standard or augmented leads were noted after repeated embolizations in three pigs (pigs 4 to 6) Changes were most prominent in the leads of the inferior surface (Leads II III and aV$_F$) Coronary flow was increased in each of the pigs that showed electrocardio-graphic changes. The partial pressure of oxygen in arterial blood was 62 mm Hg or less in each of those pigs.

The effect of the improvement of ar terial oxygenation by breathing increased amounts of oxygen after pulmonary em bolization was observed in three hypoxic pigs (Fig 3) Arterial oxygenation could not be improved in four pigs, and one pig died before oxygen was given. In pigs 1 6 and 8 the partial pressure of oxygen in arterial blood was increased to at least 76 mm Hg Right coronary flow decreased toward control levels in each pig after hypoxemia was corrected. Resistance in the right coronary arterial bed increased Pulmonary arterial mean pressure de

The t test for paired observations of small samples was used for all calculations of probability

†This was partially related to wide range of control values due to particularly high control coronary resistance in one pig If that pig were eliminated, then the reduction coronary resistance after repeated embolizations would have been significant ($P < 0.01$) The reason is not apparent for the low control right coronary flow and relatively high femoral arterial pressure causing high calculation of resistance in that pig Right coronary flow increased from to 40 ml. per minute following pulmonary embolization (that animal

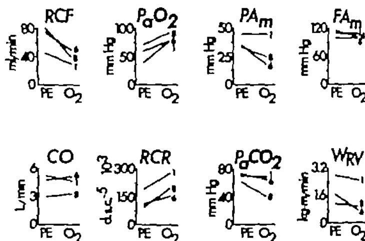


Fig 3 Pigs 1 6 and 8 Effect of correction of hypoxia after repeated pulmonary embolization (PE) by breathing increased amounts of oxygen (O_2) the partial pressure of oxygen in arterial blood (P_aO_2) rose to 76 mm Hg or higher Right coronary mean flow (RCF) decreased and right coronary resistance (RCR) increased in each pig P lmonary arterial mean pressure (PA_m) decreased in two and remained unchanged in one pig Femoral arterial mean pressure (FA_m) and cardiac output (CO) showed little change. Right ventricular work (W_{RV}) decreased The partial pressure of carbon dioxide in arterial blood (P_aCO_2) showed a slight decrease in two pigs and prominent decrease in one pig

creased in two pigs and did not change in one Right ventricular work decreased The partial pressure of carbon dioxide in arterial blood showed a slight decrease in two pigs and a prominent fall in one Femoral arterial mean pressure cardiac output heart rate and arterial blood pH showed variable and small changes. Electrocardiographic changes (T wave inversion) became less prominent in the only pig in this group that showed an abnormal electrocardiogram

Discussion

Right coronary blood flow increased after acute pulmonary embolization and was greater after larger quantities of emboli were administered than after smaller quantities. Increased right coronary blood flow has been shown by other techniques after pulmonary embolization with 5 per cent starch solutions[1] and autologous blood clots.[11] These studies, using Rb^{86} showed greater right coronary flow in dogs after pulmonary embolization than in comparable control groups. Since the completion of the present study others have also reported increased right coronary blood flow after experimental pulmonary embolization[12]

Left coronary flow in dogs has also been shown to increase after acute experimental pulmonary embolization.[4,11] This was shown by Guzman and associates[4] ... Love and O Meallie[11] using Rb^{86} by ... of us in a previous study using an electromagnetic flowmeter[4] and by the ... study of Bonanno and associates[8] ... coronary sinus drainage and an electromagnetic flowmeter Others have reported variable changes or diminished coronary flow[14] after acute pulmonary embolization Hackel and associates,[14] using the nitrous oxide method found an increase ... coronary blood flow in six dogs and a decrease in three after embolization with lycopodium spores. Feruglio and associates,[15] using the nitrous oxide method, found diminished coronary flow after pulmonary embolization with barium sulfate suspensions. The diminished coronary flow observed in some of the animals in this study may have been attributable to the terminal hypotensive phase of pulmonary embolism.

Studies of coronary flow after pulmonary embolism in closed-chest animals have shown results similar to studies of ...

Presented at the American Federation for Clinical Research, Southern Section, January 1965.

est animals.[21] The increased coronary ow after pulmonary embolization seemed be uniformly distributed throughout oth ventricles.[11] There was no significant sproportion of flow between the inner and uter surfaces of the right ventricle.[22] creased coronary flow has been shown ter pulmonary embolization with particles small enough to lodge in arterioles tarch granules[11]) and after embolization ith larger particles (polystyrene beads nd blood clots[4,21,23]). Chemical substances leased from blood clot emboli did not em to play an essential role in the control coronary blood flow since embolization ith polystyrene beads and starch granules[22] caused similar results.

The increased coronary flow observed this study and by others[4, 23] after pulmonary embolization denies the occurrence of reflex spasm in the coronary teries initiated by pressure changes in e pulmonary arteries. Reflex coronary terial spasm had been suggested as one f the possible causes of myocardial ischemia after pulmonary embolism.[24] This ossibility was supported by evidence of higher survival rate and less frequent ccurrence of ectopic rhythms in animals which pulmonary embolism was induced fter bilateral cervical vagotomy and a eneficial effect of atropine on the course f pulmonary embolism.[4]

The increased right coronary flow observed in this study also denies the occurrence of right ventricular strain as a cause f an impediment of right coronary flow fter pulmonary embolization.[24] The theory of right ventricular strain postulated hat increased right ventricular pressure as associated with diminished coronary lood flow perhaps due to extravascular ompression of the Thebesian veins and nterference with emptying of the coronary inus and veins. Earlier experimental tudies supported this concept. More ecent studies have shown increased left nd right coronary flow following elevated ressures in the right ventricle induced by mechanical constriction of the pulmonary rtery[7] and by distention of the right ventricle[1] as well as by pulmonary embolism.[11-23]

The mechanism by which right coronary flow increased after acute pulmonary embolization is not established. The observed changes after embolizations severe enough to cause arterial hypoxemia may have been related to the hypoxemia. Hypoxemia is known to increase coronary flow under other circumstances.[1, 22] Right coronary flow decreased toward control levels as hypoxemia was eliminated by the administration of oxygen. This suggests that arterial oxygenation contributed to the regulation of coronary blood flow under these circumstances although its effect may have been indirect.

Increased right coronary flow after pulmonary embolization may have been related to increased pressure in the right ventricle and increased work of the right ventricle. Gregg and associates[7] showed increased flow in the right coronary artery following mechanical constriction of the pulmonary artery. Cross showed increased flow in the right coronary artery following distention of the right ventricle. The presence of a vasodilatory reflex or local myocardial factor has been postulated by some investigators.[12]

Increased levels of carbon dioxide in arterial blood after repeated pulmonary embolizations perhaps contributed to the increased right coronary flow.[22] It is unlikely that changes in the partial pressure of carbon dioxide in arterial blood contributed to the increased coronary flow after initial embolizations. The average partial pressure of carbon dioxide in arterial blood increased only to 41 mm. Hg after that quantity of emboli. According to Feinberg and associates[22] similar small changes of carbon dioxide in arterial blood do not cause a change of coronary flow.

It is unlikely that the decrease of arterial blood pH from an average of 7.46 units to 7.32 units contributed to the increased coronary flow observed after pulmonary embolization. Severe acidosis (pH 7.08) has been reported to cause increased coronary flow.[23] However, subsequent studies of intact dogs have shown a decreased coronary flow due to acidosis.

Summary

Right coronary arterial blood flow was measured by means of an electromagnetic flowmeter during acute pulmonary embolism in open-chest anesthetized pigs

This study was undertaken in order to determine whether or not acute pulmonary embolism causes an impediment of right coronary flow which may be responsible for myocardial ischemia. Pulmonary embolism was induced with autologous blood clots in amounts sufficient to produce pulmonary hypertension but not sufficient to produce shock. No reduction of right coronary blood flow after pulmonary embolization was observed. To the contrary average right coronary mean flow increased from 27 to 61 ml per minute ($P < 0.001$) following pulmonary embolizations in quantities sufficient to increase the average pulmonary arterial mean pressure from 12 to 42 mm Hg. Smaller embolizations were associated with smaller increases or no change in right coronary mean flow. These observations are contrary to the theories of pulmonocoronary reflex spasm and right ventricular strain which had been proposed as possible causes of diminished coronary flow and subsequent myocardial ischemia after pulmonary embolism. The results suggest that myocardial ischemia in acute pulmonary embolism is not produced by an impediment of right coronary blood flow.

The authors wish to thank Dr Lewis Dexter for his encouragement and advice in this study.

REFERENCES

1. Horn, H Dack, S and Friedberg C. K. Cardiac sequelae of embolism of the pulmonary artery Arch I t. Med. 64:296, 1939
2. Dack S Master A M Horn, H Grishman A., and Field L. E. Acute coronary insufficiency due to pulmonary embolism, Am J Med. 7:464 1949
3. Cutforth, R. H nd Oram, S. The electrocardiogram i pulmonary embolism, Brit. Heart J 20:41 1958.
4. Weber D M and Phillips, J H. J A reevaluation of electrocardiographic changes accompanying acute pulmonary embolism Am. J M Sc. 251:381 1966.
5. Currens J and Barnes, A. R. The heart in pulmonary embolism Arch. I t. Med. 71:325 1943.
6. Stein, P D Alshabkhoun, S., H tem, C., Shahriari, A. A. P H ynes, F W Harken, D E., and Dexter L. Coronary artery blood flow in acut pulmonary embolism, Am J Cardiol. 21:32, 1968.
7. Aviado, D M The lung circulation, Oxford, 1965 Pergamon Press, Ltd., Vol. II p. 696.
8. Case, R. B Roselle H A., and Nassar, [illegible] Simplified method for calibration of electromagnetic flow meters, M Res. Eng [illegible]
9. Gregg D E. Coronary circulation in h[illegible] and disease Philadelphia, 1950, Lea & F[illegible] Publishers.
10. Dexter L., Whittenberger J L., [illegible] W., Goodale, W T Gorlin, R., and [illegible] C. G : Effect of exercise on circulatory [illegible]namics of normal individuals, J Appl. Phy[illegible] 3:439 1951
11. Gurman S. V Chavez, F R., and [illegible] E. S. Myocardial blood flow after experimental pulmonary embolism in the [illegible] Am Heart J 68:66, 1964
12. Love, W D and O'Meallie, L P [illegible] in coronary blood flow in the right [illegible] ventricle in response to an acute [illegible] hemodynamic load, J Lab. & Cl[illegible] 62 72 1963
13. Bonanno, J A., Blalock, G R., Jr [illegible] O and Symbas, P N Coronary blood [illegible] in acute experimental pulmonary embolization Am. J Cardiol. 21:91 1968 (abstr.)
14. Hackel, D B Kinney T D and Gor[illegible] W T : Cardiovascular effects of pulmonary embolization in intact dogs studied by [illegible] catheterization of the coronary sinus, Am J Physiol. 176 135, 1954
15. Ferugfio, F S., Mighela, B Campa[illegible] Pandolfo, G., and Bert, G. La portata [illegible]narica e renale nell'embolia polmonare [illegible]mentale, Minerva Cardioangiol 9:[illegible]
16. Malinow M R., Katz, L N and [illegible] Is there a pulmonocoronary reflex in pulmonary embolism? Am. Heart J 31:702, 1946
17. Gregg D E. Pritchard, W H Shipley [illegible] E., and Wearn, J T Augmentation of [illegible] flow in the coronary arteries [illegible] right ventricular pressure Am. J. Phy[illegible] 139 726, 1943.
18. Cross, C. E. Right ventricular pressure [illegible] coronary flow Am. J Physiol. [illegible]
19. Berne, R. M Blackmon, J R and Gar[illegible] T H Hypoxemia and coronary blood [illegible] J Clin. I vest. 36 1101 1957
20. Feinberg H., Gerola, A., and Katz, L [illegible] Effect of hypoxia on cardiac oxygen con[illegible] tion and coronary flow Am. J Physiol [illegible] 1958.
21. Scott, J C., Finkelstein, L J and [illegible] N Effects of hypoxemia on coronary [illegible] flow and cardiac output in normal and [illegible] thyroid dogs, Am J Cardiol. 10:[illegible]
22. Feinberg H Gerola, A., and Katz, L [illegible] Effect of changes i blood CO_2 level on [illegible] nary flow and myocardial O_2 con[illegible] Am. J Physiol. 199:349 1960.
23. Eckenhoff J E., Hafkenschiel, J H [illegible] Landmesser C. M The coronary circulation in the dog Am. J Physiol. 148:582, [illegible]
24. Goodyer A. V N Eckhardt, W F [illegible] R. H and Goodkind, M J : Effect of [illegible] bolic acidosis and alkalosis on coronary [illegible] flow and myocardial metabolism in the [illegible] dog, Am. J Physiol 200:628, 1961.

Computation of a variable location dipole representation from body surface leads

Robert A. Helm, M.D.
Te-Chuan Chou, M.D.
Cincinnati, Ohio

A physical dipole consists of a positive source of current and a nearby equal but negative source of current, the latter often being referred to as a sink. In the case of a mathematical dipole, the distance between the source and sink approaches zero as a limit, while the current concomitantly increases so that the product of current times distance is not changed. A physical dipole and a mathematical dipole thus differ only in that, at any instant, the latter can be assumed to be located at a single point. Einthoven and associates[1] introduced the concept that the electrical activity of the heart may be represented by a mathematical dipole which varies from instant to instant in its strength and in the directional orientation of its positive and negative poles. For the sake of simplicity, Einthoven and co-workers imposed the restriction that the location of the dipole does not vary from instant to instant, but rather remains fixed at a single point throughout the cardiac cycle. The concept of a fixed location dipole as an equivalent cardiac generator has achieved popularity because of its simplicity rather than its accuracy in mimicking the electrical characteristics of the heart. If a mathematical dipole of variable strength and variable orientation is also permitted to vary in its location from instant to instant throughout the cardiac cycle, an important limitation of the fixed dipole representation is removed. The purpose of this paper is to describe a method of computing the variable strength, the variable orientation, and the variable location of a single dipole from multiple lead voltages recorded simultaneously on tape and subsequently digitized.

Derivation of method

If n independent leads are considered, the following n simultaneous equations* may be written for any given instant of the cardiac cycle and for any given dipole location:

$$p_1 = x_1X + y_1Y + z_1Z + E_1 \qquad (1)$$

$$p_2 = x_2X + y_2Y + z_2Z + E_2 \qquad (2)$$

$$= \quad Y + \quad Y + \quad Z +$$

$$p_n = x_nX + y_nY + z_nZ + E_n \qquad (3)$$

The terms p_1, p_2, … and p_n repre-

From the Cardiac Laboratory, Cincinnati General Hospital, and the Department of Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

This work was supported in part by the Mabel S. Stonefield Fund for Vectorcardiographic Research, College of Medicine, University of Cincinnati, and by funds received from the Heart Association of Southwestern Ohio, Cincinnati, Ohio.
Received for publication June 19, 1959.

*In these and all subsequent equations, capital letters represent unknown values to be calculated, and small case letters represent known or measured values.

sent the measured voltages recorded at the given instant by each of the n leads. The terms (x_1, y_1, and z_1), (x_2, y_2, and z_2) ( ) and (x_n, y_n, and z_n) represent the orthogonal components of the lead vectors of the n leads. These are assumed to be known and to remain constant throughout the cardiac cycle. The capital letters X, Y, and Z represent the unknown orthogonal components of the dipole vector at the instant under consideration. E_1, E_2, and E_n represent unknown errors at this same instant in each of the n equations when n exceeds three. If the E terms were omitted, X, Y, and Z calculated from one group of three equations would usually differ from X, Y, and Z calculated from another group of three equations; the discrepancy would result from the fact that the n leads are independent, that is, they are formed by not less than $(n + 1)$ separate electrode placements. The introduction of the E terms permits X, Y, and Z to remain constant in all of the n simultaneous equations. It is apparent that the E terms increase the number of unknowns to $(n + 3)$ so that X, Y, and Z cannot be calculated directly from the n simultaneous equations. However, unique values for X, Y, *and* Z *exist if an additional condition* is imposed, namely, that the E terms be minimized in some suitable manner. To accomplish this, it is advantageous first to divide both sides of each rearranged equation by its respective value of p.

$$\frac{E_1}{p_1} = 1 - \left(\frac{x_1}{p_1}\right)X - \left(\frac{y_1}{p_1}\right)Y - \left(\frac{z_1}{p_1}\right)Z \quad (4)$$

$$\frac{E_2}{p_2} = 1 - \left(\frac{x_2}{p_2}\right)X - \left(\frac{y_2}{p_2}\right)Y - \left(\frac{z_2}{p_2}\right)Z \quad (5)$$

$$= 1 - (\ )X - (\ )Y - (\ )Z$$

$$\frac{E_n}{p_n} = 1 - \left(\frac{x_n}{p_n}\right)X - \left(\frac{y_n}{p_n}\right)Y - \left(\frac{z_n}{p_n}\right)Z \quad (6)$$

This division is carried out so as to weigh the instantaneous E values in accordance with the measured p values at each instant. Such a corrective measure prevents distortion of X, Y, and Z values calculated from equations (11), (12), and (13) described below, which would result from E values being large merely as the result of their leads having large voltages as opposed to the E terms being critically large.

If equations (4) through (6) are squared and subsequently summated, equation (7) is obtained.

If the partial derivative of $\sum\left(\frac{E^2}{p^2}\right)$ is taken with respect to X, with respect to Y, and with respect to Z, three simultaneous equations are obtained (8) through (10).

When each partial derivative is zero, $\sum\left(\frac{E^2}{p^2}\right)$ is minimal. Rearranging and simplifying equations (8), (9), and (10), equations (11) through (13) are obtained.

$$\sum\left(\frac{E^2}{p^2}\right) = n - 2\sum\left(\frac{x}{p}\right)X - 2\sum\left(\frac{y}{p}\right)Y - 2\sum\left(\frac{z}{p}\right)Z + \sum\left(\frac{x^2}{p^2}\right)X^2 + 2\sum\left(\frac{xy}{p^2}\right)XY$$
$$+ 2\sum\left(\frac{xz}{p^2}\right)XZ + \sum\left(\frac{y^2}{p^2}\right)Y^2 + 2\sum\left(\frac{yz}{p^2}\right)YZ + \sum\left(\frac{z^2}{p^2}\right)Z^2 \quad (7)$$

$$\frac{\partial\sum\left(\frac{E^2}{p^2}\right)}{\partial X} = -2\sum\left(\frac{x}{p}\right) + 2\sum\left(\frac{x^2}{p^2}\right)X + 2\sum\left(\frac{xy}{p^2}\right)Y + 2\sum\left(\frac{xz}{p^2}\right)Z = 0 \quad (8)$$

$$\frac{\partial\sum\left(\frac{E^2}{p^2}\right)}{\partial Y} = -2\sum\left(\frac{y}{p}\right) + 2\sum\left(\frac{xy}{p^2}\right)X + 2\sum\left(\frac{y^2}{p^2}\right)Y + 2\sum\left(\frac{yz}{p^2}\right)Z = 0 \quad (9)$$

$$\frac{\partial\sum\left(\frac{E^2}{p^2}\right)}{\partial Z} = -2\sum\left(\frac{z}{p}\right) + 2\sum\left(\frac{xz}{p^2}\right)X + 2\sum\left(\frac{yz}{p^2}\right)Y + 2\sum\left(\frac{z^2}{p^2}\right)Z = 0 \quad (10)$$

$$\sum\left(\frac{x^2}{\rho^2}\right)X+\sum\left(\frac{xy}{\rho^2}\right)Y+\sum\left(\frac{xz}{\rho^2}\right)Z=\sum\left(\frac{x}{\rho}\right) \quad (11)$$

$$\sum\left(\frac{xy}{\rho^2}\right)X+\sum\left(\frac{y^2}{\rho^2}\right)Y+\sum\left(\frac{yz}{\rho^2}\right)Z=\sum\left(\frac{y}{\rho}\right) \quad (12)$$

$$\sum\left(\frac{xz}{\rho^2}\right)X+\sum\left(\frac{yz}{\rho^2}\right)Y+\sum\left(\frac{z^2}{\rho^2}\right)Z=\sum\left(\frac{z}{\rho}\right) \quad (13)$$

By solving simultaneous equations (11), (12) and (13) unique values are obtained for X, Y, and Z which minimize $\sum\left(\frac{E^2}{\rho^2}\right)$ for the dipole location under consideration at the given instant of time.

If there are m dipole locations for which m sets of x, y, and z values are known for the n leads, X, Y, and Z are calculated for each of the m locations and from these calculated values, the m sets of values of $\sum\left(\frac{E^2}{\rho^2}\right)$ are computed from equation (7). That dipole location which yields the lowest $\sum\left(\frac{E^2}{\rho^2}\right)$ is selected by the computer and its corresponding X, Y, and Z values are also selected. If the entire process is then repeated for each digitized instant of time, the varying dipole location and the varying X, Y, and Z components (defining dipole strength and directional orientation) become manifest. These values are optimal, yielding the best fit of the digitized instantaneous voltages recorded by each of the n leads.

Discussion

That computers will play an increasingly important role in electrocardiographic interpretation is becoming apparent. Equipment is now available for converting taped simultaneously recorded lead voltages to digital form for rapid analysis in the computer laboratory. Such facilities provide practical means of applying the concept of a variable location dipole representation to electrocardiography. At the present time there is only limited published lead vector data for multiple leads and multiple dipole locations as determined experimentally on torso models. However, methods of obtaining such data are established so that the x, y, and z components of lead vectors for many leads and many dipole locations could be systematically determined on torso models having a variety of configurations for men and women and for adults and children. The body configuration of any particular patient being studied could be matched to a similar torso model for which complete x, y, and z lead vector data would be stored and programmed for rapidly and repeatedly computing X, Y, and Z from equations (11), (12), and (13), and also repeatedly calculating $\sum\left(\frac{E^2}{\rho^2}\right)$ from equation (7). Pairs of the calculated orthogonal dipole components could be plotted on a cathode ray tube to form frontal (XY), sagittal (ZY), and transverse (XZ) planar vector cardiographic loops representing the termini of the consecutive dipole vectors. Loops representing the time course of the origins of the consecutive dipole vectors on the frontal, sagittal, and transverse planes could also be plotted on the cathode ray tube. In addition to providing the optimal dipole strength and direction and the optimal dipole location at each of the digitized instants of time, the method described herein yields information concerning the errors involved in the computations at each of the digitized instants. For instance, $\sum\left(\frac{E^2}{\rho^2}\right)$ is available at each instant, and this summation of the squares of the relative errors of each lead might be more meaningfully expressed by dividing the number of leads, n, into the square root of $\sum\left(\frac{E^2}{\rho^2}\right)$. It is also possible to calculate the individual values of E for each lead by substituting the computed orthogonal components, X, Y, and Z of the dipole vector in equations (1) through (3) at each instant. The scalar configuration of

the voltages of each lead could then be plotted simultaneously with the scalar configuration of each lead's errors from instant to instant

It is of interest to consider the number of degrees of freedom involved in the variable location dipole representation. At each instant the orthogonal components defining the magnitude and direction of the spatial dipole vector represent three degrees of freedom. The location of the dipole at each instant might seem to involve three additional degrees of freedom in that this location can also be expressed conveniently in terms of orthogonal components, e.g. the X, Y, and Z distances from the center of the volume conductor. However, the dipole location is dependent on the selection of one of m possible locations for which lead vectors are known for each of the n leads utilized. There is, therefore, only one rather than three additional degrees of freedom. Nevertheless, the number of independent leads required to define both the instantaneous dipole vector and also the instantaneous dipole location need not be limited to four. Indeed, the accuracy obtained in calculating the dipole vector and in selecting the dipole location at each instant is enhanced by the utilization of as many leads as practical including particularly leads which would be expected to emphasize nonfixed dipolar voltages. The only limiting factors are the accuracy of electrode placement and the accuracy of lead vector data obtained from models with somewhat different body configurations and different internal impedances than those of the patient. As physicists make improved measurements on more sophisticated models with heterogeneous impedances simulating those of intact man, lead vector data will be realistically improved.

The invalidity of summating a myriad of widely separated active dipoles into a single resultant dipole is diagrammatically illustrated and discussed elsewhere.[3] It should be emphasized that such a summation is neither made nor assumed in the computation described herein. Rather the variable location dipole represents [illegible] *equivalent* generator which simulates the electrical activity of the heart only in the sense that the dipole's electrical [illegible]ties are optimally consonant with the recorded body surface voltages. In [illegible]ing any type of equivalent generator [illegible] assumption is made concerning the [illegible]mental nature of the actual cardiac generator

Summary

A computer method is described which permits the use of a variable location dipole rather than a fixed location [illegible] as the equivalent generator for the representation of the electrical activity of the heart. The following data are obtained from digitized voltages of at least four or preferably as many independent leads as can be simultaneously recorded

1 The orthogonal components which define at each digitized instant, the optimal spatial location of the single dipole

2 The orthogonal components which define at each digitized instant, the optimal strength and direction of this dipole.

3 The mean error involved in obtaining the best fit of the digitized voltages of the simultaneously recorded leads, and the individual errors of each of these leads at each digitized instant of time.

REFERENCES

1 Einthoven, W., Fahr, G., and deWaart, A.: Über die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Electrokardiogramms [illegible] ges Physiol. 150:275, 1913. Translation [illegible] H. E., and Sekelj, P.: On the direction and manifest size of the variations of potential in the human heart and on the influence of the position of the heart on the form of the electrocardiogram. Am. Heart J. 40:163, [illegible]

2. Frank, E.: Determination of the [illegible] center of ventricular depolarization in the human heart, Am. Heart J. [illegible]

3 Chou, T. C., and Helm, R. A.: Clinical vectorcardiography. New York, 1967, Grune & Stratton, Inc., p. 5.

Myocardial K^+ loss after countershock and the relation to ventricular arrhythmias after nontoxic doses of acetyl strophanthidin

Timothy J. Regan, M.D.
Angel Markov, B.S.
Henry A. Oldewurtel
Maureen A. Harman, M.D.
Jersey City, N. J.

An enhanced sensitivity of the digitalized heart to ventricular arrhythmias during cardioversion has been well established.[1] It has been suggested that electric countershock, used in terminating supraventricular arrhythmias, may reveal latent digitalis intoxication even when there has been no previous evidence of digitalis excess.[2] Since ventricular arrhythmias that arise from experimental digitalis intoxication appear to be related to enhanced potassium (K) egress from the heart, it was reasoned that the sensitivity of the digitalized heart may be related to an effect of cardioversion on potassium transport in the myocardium. To explore this view, a series of normal animals received direct-current countershock at a relatively low energy level. In another series acetyl strophanthidin was administered at a nontoxic dose level and countershock was applied during the period of positive inotropic activity of this drug, and compared with a group receiving strophanthidin alone.

Methods

Male mongrel dogs weighing 18 to 24 kilograms were anesthetized 18 hours postprandial with morphine sulfate, 3 mg per kilogram, and pentobarbital (Nembutal) 12 mg per kilogram and studied without opening the chest. After insertion of an endotracheal tube, respiration was regulated with a Harvard respiratory pump which facilitated the maintenance of arterial oxygen saturation and pH in the normal range. Catheters were placed in the coronary sinus, aorta, and left ventricle for blood sampling and pressure determinations. Myocardial blood flow was measured at 3 to 4 minute intervals by injection of Kr^{85} into a coronary artery catheter[4] or retrograde into the coronary sinus. Catheters were initially filled with diluted heparin and thereafter

From the Department of Medicine, New Jersey College of Medicine and Dentistry, and the Thomas J. White Cardiopulmonary Institute, B. S. Pollak Hospital for Chest Diseases, Jersey City, N. J. 07304.
Supported in part by United States Public Health Service grants HE [illegible], HE [illegible], and HE [illegible] and grants from the American and New Jersey Heart Associations.
Dr. Regan is Professor of Medicine; Mr. Markov, research assistant; M. Oldewurtel, research associate in medicine; and Dr. Harman, Fellow in Medicine.
Received for publication June 24, [illegible].
*This work was done during the tenure of an Established Investigatorship of the American Heart Association.

were maintained patent by slow saline infusions or intermittent flushes. Paired sampling of arterial and coronary venous blood was performed at stated intervals for analysis of sodium as well as potassium in view of the role of the former in the generation and propagation of the action potential. Net ion transfer in the myocardium was calculated from the product of coronary plasma flow and the arterial coronary sinus difference of potassium and sodium in those animals whose coronary blood flow and arterial ion concentration remained relatively constant within the 12 per cent error for the flow method and 3 per cent for ion analysis. Five animals failed these criteria and were excluded from the study.

Plasma potassium and sodium determination were performed on a Technicon autoanalyzer and flame-photometer attachment. Only samples without significant hemolysis were used. Arterial pH was determined on a Beckman meter at 37° C and hematocrit by the glass capillary method. Donor animals were used for blood replacement after each blood sampling. Ventricular and aortic pressures were measured through 50 cm Goodale-Lubin catheters connected directly to Statham strain gauge transducers, P23 Db. The pressures standard Lead II and a filtered Lead II of the electrocardiogram were continuously monitored with an Electronics for Medicine DR-8 recorder. A beat was considered ectopic if the QRS complex was aberrant in form or not in proper temporal relation to the preceding P wave and if the following T wave was aberrant. Ectopic beats were [illegible] for immediately following countershock [illegible] the recording obtained from the [illegible] Lead II of the electrocardiogram.

A D C defibrillator manufactured by the Electrodyne Co. (Model DS-95M) was used for all experiments. This device [illegible] synchronized to discharge 20 to 30 [illegible] after the peak of the R wave from Lead II. We chose to deliver the pulse at this [illegible] rather than during diastole, because [illegible] of electrical pulses appear to be less [illegible] this phase of the cardiac cycle. In all [illegible] mals two defibrillatory electrode paddles measuring 9 cm. in diameter were covered with conductive paste and applied [illegible] pressure on either side of the chest at the level of the apex thrust. The energy of the electrical discharge was set at a [illegible] level of 75 watt-seconds. Ten [illegible] (Group I) received a single transthoracic capacitor discharge, and six of these [illegible] repeated countershock applications at [illegible] watt-seconds, using intervals of 60 [illegible]

Group II consisting of eight [illegible] received acetyl strophanthidin, 0.03 [illegible] per kilogram (donated by Dr. G. C. [illegible] of Eli Lilly & Co. Indianapolis, Ind.) a dose which was previously found [illegible] produce a positive inotropic response [illegible] the left ventricle without arrhythmias. Group III, eight dogs, received the [illegible] dose of this digitalis preparation, followed by a transthoracic electrical discharge 4 to 5 min. later when the drug's [illegible] inotropic activity was present.

An index of left ventricular contraction was deduced from changes in the first derivative of the left ventricular pressure [illegible]

Table I. Hemodynamic response to countershock

	Control	*1-2 min*	*3 min*
LV dp/dt max. (mm. Hg/sec.)	2,420 ± 28	2,807 ± 36	2,4[illegible] ± [illegible]
LV end-diastolic pressure (mm. Hg)	6.5 ± 0.4	6.1 ± 0.7	6.6 ± [illegible]
Heart rate/min	132 ± 11	130 ± 12	13[illegible] ± [illegible]
Mean aortic pressure (mm. Hg)	118 ± 7	116 ± 6	120 ± [illegible]
Coronary blood flow (ml./100 Gm./min.)	93 ± 3	94 ± 3	91 ± [illegible]

dp/dt) in the presence of an unaltered eart rate aortic pressure and left ventricular end-diastolic pressure. The first derivative was computed on an R-C differentiating circuit and converted into mm Hg per second.[9] Ventricular diastolic pressure was recorded at sufficient sensitivity so that 1 mm Hg equalled 5 mm of paper. Measurements were made at the end expiration phase of the respiratory cycle. Statistical variations are expressed as standard errors and Student's t test was paired or nonpaired as appropriate.

Results

The application of transthoracic countershock in Group I at an energy level of 75 watt-seconds was associated with minimal ectopic activity averaging 2.7 beats in the immediate postcountershock period. After half a minute there was no significant difference in the heart rate and aortic pressure from controls (Table I). However there was a small transient, but significant increase in the first derivative of left ventricular pressure in the presence of an unchanged ventricular end-diastolic pressure ($p < 0.01$). Sequential coronary blood flow measurement and the arterrovenous (A-V) differences of sodium did not show significant change from control. The first samples after application of countershock had increased concentrations of potassium in the coronary sinus without significant change of arterial concentrations. This alteration persisted as long as nine minutes

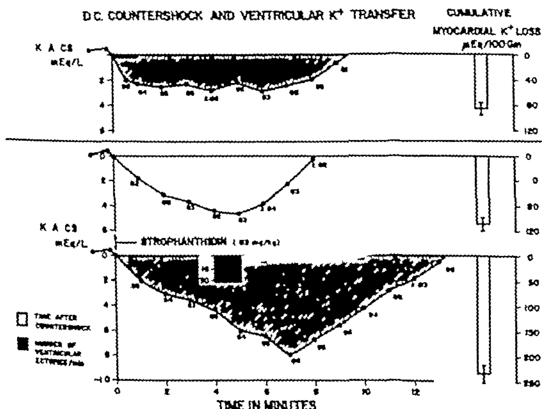


Fig. 1. The upper panel represents the net loss of potassium ion immediately after the transthoracic electrical discharge and the black bar in the first minute indicates the brief period when isolated ectopic beats were observed. The middle panel demonstrates the K loss from the myocardium in animals treated with a nontoxic dose of acetyl strophanthidin. The lower panel indicates the enhanced loss of this ion after the same dose of strophanthidin in another group when countershock was applied four minutes after drug administration and was associated with significant ventricular ectopic activity. The columns to the right indicate the cumulative K loss derived from the product of myocardial blood flow and the A-V difference of potassium.

when the A V difference concentrations reverted to virtually control levels (Fig 1) The cumulative loss of this ion from myocardium estimated from the product of the arteriovenous differences and coronary plasma flow was 82 μEq per 100 Gm A similar K^+ loss was seen in the six animals shocked a second and third time at 60 min intervals. The average K^+ loss after the second countershock was 78 ± 9 μEq per 100 Gm and 83 ± 9 μEq per 100 Gm on the third occasion

Administration of acetyl strophanthidin 0 03 mg per kilogram to the second group of animals was associated with no evidence of arrhythmias. The first derivative of left ventricular pressure increased to a maximum of 78 per cent between the fourth and sixth minute after drug administration The cumulative potassium loss from the myocardium during the activity of the drug averaged 119 μEq per 100 Gm whereas neither uptake or loss of sodium was observed to a significant degree

In the third group of animals when the countershock intervention was introduced between four and five minutes after the administration of strophanthidin there was an increase in the rate of potassium loss over that seen in Group II in the same time period ($p < 0.02$) and the net loss of potassium persisted for a longer period of time without significant sodium change. There was an associated increase of ectopic activity which was most prominent in the immediate countershock period averaging 30 ventricular ectopics in the first minute with progressive disappearance thereafter

Discussion

Production of ventricular ectopic beats in the postcountershock period has been related to the quantity of energy applied across the chest of the intact animal The minimal ectopic activity seen in the animals of Group I is consistent with that previously observed in the nondigitalized animal at the energy level applied[2] The mechanism for the enhanced rhythmicity of ventricular tissue during this immediate postcountershock period is not known It is conceivable that the potassium loss observed in the subsequent minutes may represent an extension of a more [illegible] displacement of potassium ion at the [illegible]ment of countershock application, [illegible] would not be demonstrable by the [illegible] of this study

It has been suggested that [illegible] adrenergic activity may explain the [illegible]rence of arrhythmias after countershock The increment in the first derivative of left ventricular pressure is consistent [illegible] an increase of adrenergic activity This [illegible] observed in the period after a stable [illegible] is assumed some seconds after the [illegible]tion of ectopic activity However [illegible] coronary infusion of epinephrine[11] or [illegible]inephrine[11] would indicate that in a [illegible] state situation there is uptake of potassium by the heart early during the [illegible] of these hormones. Since large doses of catecholamines may in some circumstances be associated with egress of K^+ [illegible] the positive inotropic response has [illegible]ed[11,12] a sudden short lived sympathetic stimulus during countershock may be responsible for the observed ionic [illegible]

It has been previously shown that [illegible] of digitalis compounds at toxic levels [illegible] be associated with significant [illegible]tion of the arrhythmia when low energy levels are applied to the animal. The current study indicates that the dosage levels of strophanthidin that are 60 per cent of those producing ventricular arrhythmias which in themselves are free of evidence of toxicity may be associated with significant ectopic activity when countershock is applied The enhanced net loss of potassium observed in this circumstance may serve as the basis for the ventricular ectopic foci while its reproducibility [illegible] repeated electrical shocks is in accord with the fact that the energy level required to produce ventricular tachycardia is not altered by repeated shocks[1]

An important role of the potassium [illegible] in the genesis of ectopic activity [illegible] suggested by findings during the [illegible] toxic responses to acetyl strophanthidin [illegible] and effective antiarrhythmic therapy [illegible]tricular arrhythmias that immediately [illegible] low experimental hypercapnia[13] and [illegible] after the administration of acetyl[illegible] have been similarly associated with [illegible] of K^+ from the ventricle Ectopic [illegible]

…as been observed in the late stages of a sustained infusion of epinephrine when there is egress of this ion from the ventricle[1] after the positive inotropic effect has abated. The relevance of this cation is further shown by the production of ventricular ectopic beats during intracoronary infusion of potassium chloride.[13,14] The production of ventricular ectopic beats and fibrillation by increments of extracellular K+ suggests that a net outward movement of the ion from the cell is likely to modify rhythmicity principally through its effect on the transcellular ratio.

Summary

Since ventricular arrhythmias due to digitalis appear to be related to enhanced potassium egress from the heart, it was reasoned that the sensitivity of the digitalized heart during cardioversion may be related to an effect on myocardial K transport.

The application of transthoracic countershock in normal intact anesthetized dogs, at an energy level of 75 watt-seconds produced increased concentrations of K+ in the coronary sinus for as long as nine minutes. A similar cumulative loss of this ion from myocardium estimated from the product of the A-V differences and coronary plasma flow was seen after a second or third shock.

Administration of acetyl strophanthidin 0.03 mg. per kilogram to a second group of animals was associated with no evidence of arrhythmias. The cumulative K+ loss from the myocardium during the activity of drug averaged 119 μEq per 100 Gm.

In a third group countershock intervention four minutes after the administration of strophanthidin produced an enhanced potassium loss over that seen in Group II in the same time period ($p < 0.02$). There was an associated increase of ectopic activity in the postcountershock period, supporting the view that altered K transport is the basis for this phenomenon.

Appreciation is expressed for the technical assistance of Mrs. B. Stoll and Mrs. R. Jenkins and for the secretarial services rendered by M... Bisetti and Miss K. Terracciano.

REFERENCES

1. Lown, B., Kleiger, R., and Williams, J. Cardioversion and digitalis drugs. Changed threshold to electric shock in the digitalized animals. Circulation Res. 17:519, 1965.
2. Ten-Eick, R. E., Wyte, S. R., Ross, S. M., and Hoffman, B. F. Postcountershock arrhythmias in untreated and digitalized dogs, Circulation Res. 21:375, 1967.
3. Gilbert, R., and Cuddy, R. P. Digitalis intoxication following conversion to sinus rhythm, Circulation 32:58, 1965.
4. Regan, T. J., Harman, M. A., Lehan, P. H., Burke, W. M., and Oldewurtel, H. A. Ventricular arrhythmias and K transfer during myocardial ischemia and intervention with procaine amide, insulin, or glucose solution, J. Clin. Invest. 46:1657, 1967.
5. Herd, J. A., Hollenberg, M., Thorburn, G. D., Kopald, H. H., and Barger, A. C. Myocardial blood flow determined with krypton[85] in unanesthetized dogs, Am. J. Physiol. 203:122, 1962.
6. Harman, M. A., Markov, A., Lehan, P. H., Oldewurtel, H. A., and Regan, T. J. Coronary blood flow measurements in the presence of arterial obstruction, Circulation Res. 19:632, 1966.
7. Regan, T. J., Frank, M. J., Lehan, P. H., and Hellems, H. K. Relationship of insulin and strophanthidin to myocardial metabolism and function, Am. J. Physiol. 205:790, 1963.
8. Wallace, A. G., Skinner, N. S., Jr., and Mitchell, J. H. Hemodynamic determinants of the maximal rate of rise of left ventricular pressure, Am. J. Physiol. 205:30, 1963.
9. Reeves, T. J., Hefner, L. L., Jones, W. B., Coghlan, C., Prieto, G., and Carroll, J.: The hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction, Am. Heart J. 60:745, 1960.
10. Regan, T. J., Moschos, C. B., Lehan, P. H., Oldewurtel, H. A., and Hellems, H. K. Lipid and carbohydrate metabolism of myocardium during the biphasic inotropic response to epinephrine, Circulation Res. 19:307, 1966.
11. Regan, T. J., Longon, B. L., Binak, K., and Hellems, H. K. Sympathomimetics as antagonists of strophanthidin ... and arrhythmic effects, Circulation Res. 11:17, 1962.
12. Regan, T. J., Moschos, C. B., Oldewurtel, H. A., Weisse, A. B., and Asokan, S. K. Dominance of lipid metabolism in the myocardium under the influence of l-norepinephrine, J. Lab. & Clin. Med. 70:221, 1967.
13. Brown, E. B., Jr., and Mowlem, A. Potassium loss from the heart during the immediate posthypercapnic period, Am. J. Physiol. 198:962, 1960.
14. Hano, J. E., and Harris, A. S. Effects of histamine and potassium release agents on ventricular rhythms before and after coronary occlusion, Am. Heart J. 65:368, 1963.

A simple example of the multipole theory applied to electrocardiography

Robert Plonsey Ph D
Cleveland Ohio

The application of multipole theory to electrocardiography suggested by Wilson and associates,[6] was first developed in its mathematical detail by Yeh and Martinek[4] and Yeh and associates.[7] Significant further contributions were introduced by Geselowitz[3] and Brody and associates.[2] Direct measurement of the multipole generators of a living heart was carried out by Hlavin and Plonsey. Although this work spans a decade many misconceptions remain. The purpose of this annotation is to clarify by means of a simple example the functional role of multipole cardiac generators.

Each active heart cell constitutes a dipole current source. Consequently the elementary bioelectric source unit is the dipole. For a single dipole at the origin of a coordinate system and in the z direction as illustrated in Fig 1 the potential field in a uniform homogeneous medium of infinite extent is given by

$$\Phi = \frac{1}{4\pi\sigma}\frac{p\cos\theta}{r^2} \qquad (1)$$

In equation (1) r is the distance from dipole to field point and θ is the angle between the orientation of the dipole and the direction to the field point. (In the example θ is the polar angle.)

Consider now a pair of colinear dipo[les] spaced 2A units apart as illustrated [in] Fig 2. This simple source configuration incorporates an aspect of real electro[-] cardiographic sources, namely that the dipole elements are spatially distributed. Now in clinical vectorcardiography the source would be characterized as if both dipoles were located at the origin (in which case they merge into a single dip[ole]

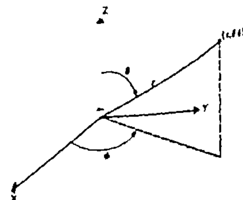


Fig 1 Single dipole [a]t origi[n]

From the Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio 44106.
This work was supported in full by the United States Public Health Service through Grant HE 10417 ... Institutes of Health.
Received for publication June 26, 1968.

double strength) In fact both electrocardiographs and vectorcardiographs seek to determine a single net fixed location dipole The field that would be generated by the vectorcardiographically determined source is

$$\Phi_{vc} = \frac{1}{4\pi\sigma}\,\frac{2p\cos\theta}{r^2} \qquad (2)$$

which is equation (1) except for the replacement of p by $2p$

Now the true field can be calculated by considering the actual distance between each dipole and the field point and the actual angle θ in each case. Referring to Fig 2 we get

$$\Phi_{ac} = \frac{p}{4\pi\sigma}\left(\frac{\cos\theta_1}{r_1^2} + \frac{\cos\theta_2}{r_2^2}\right) \qquad (3)$$

By comparing the true potential field with the field obtained from the fixed equivalent dipole one obtains a measure of the approximate nature of the latter Such a comparison is given in Fig 3 for field points on a spherical surface whose radius equals the dipole spacing (The latter condition roughly approximates the extent

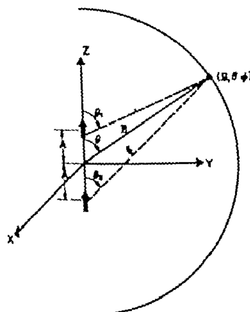


Fig 2 Geometry for two colinear dipoles equispaced from origin.

of the bioelectric sources in the heart as equal to the source torso surface distance.) The discrepancy between the two is fairly clear

According to multipole theory any arbitrary distribution of dipoles generates a field which, beyond an enclosing spherical surface, can *always* be written as

$$\Phi_{mult} = \frac{1}{4\pi\sigma}\sum_{n=0}^{\infty}\sum_{m=0}^{n}\left[a_{nm}P_n^m(\cos\theta)\cos m\phi + b_{nm}P_n^m(\cos\theta)\sin m\phi\right]\frac{1}{r^{n+1}} \qquad (4)$$

where $P_n^m(\cos\theta)$ are polynomials in the argument $(\cos\theta)$. All that is required for equation (4) to converge to a specified field is to appropriately choose the numerical constants a_{nm} and b_{nm}. Now for the two dipole model illustrated in Fig 2 symmetry demands that there be no potential variation with azimuth angle ϕ Consequently we can infer that application of equation (4) to this specific problem will require that $m = 0$ only Thus, the multipole equivalent of equation (3) valid for $r > A$ is

$$\Phi_{ac} = \frac{1}{4\pi\sigma}\sum_{n=0}^{\infty} a_n P_n(\cos\theta) \qquad (5)$$

Equation (5) is precisely the same as (3) for $r > A$ (assuming that the a_n are chosen to reflect the actual source geometry) Writing out the first three terms of (5) for the source described by Fig 2 gives (see Stratton for details)

$$\Phi_{ac} = \frac{p}{4\pi\sigma}\left(\frac{2\cos\theta}{r^2} + \frac{5\cos^3\theta - 3\cos\theta}{r^4} + \frac{63\cos^5\theta - 70\cos^3\theta + 15\cos\theta}{4r^6} + \cdots\right) \qquad (6)$$

If we examine equation (6) we note that the leading term corresponds precisely to the source defined by vectorcardiographic measurements namely the fixed location dipole What is significant about equation (6) is that it includes additional terms which when added to the dipole term give a result which more closely approximates the actual potential. The greater the number of terms of the series the more closely the actual potential is approximated. The first correction term

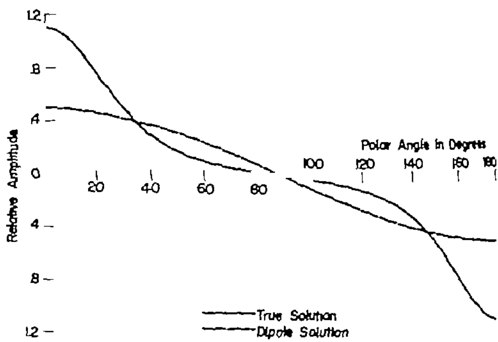


Fig. 3 Exact field and equivalent single dipole field of the two colinear dipole "heart" source (described in Fig. 2) B/A = 2

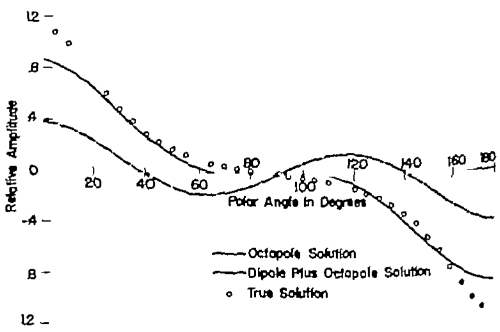


Fig. 4 The potential field of the octapole and dipole plus octapole component of the two colinear dipole "heart" source and the exact field solution. B/A = 2 in Fig. 2.

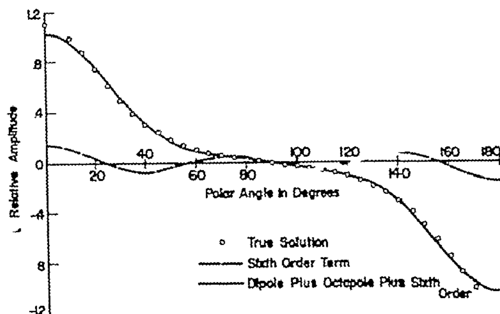


Fig. 5 The potential field of the sixth order multipole component and multipole components summed through sixth order of two collinear dipole "heart" source, and the exact field solution B A = 2 in Fig 2

characterized by 1 r^4 behavior is called the octapole.

The nature of the contribution of these terms is illustrated in Figs. 4 and 5 In Fig. 4 the octapole term alone is plotted for the conditions assumed in Fig 2 Note that it provides a spatial *third harmonic* (compare to the dipole [alone] term shown in Fig. 3) Note further how the dipole plus octapole is a much improved approximation to the true potential field. In Fig 5 the 1 r^6 (alone) term is seen to correspond to a spatial fifth harmonic† Its inclusion, along with the dipole and octapole makes for a potential field that is difficult to distinguish from the true field

Although the example chosen is a simple one, the following conclusions can be generalized

1 The leading (dipole) term of the multipole expansion corresponds exactly to the fixed location dipole of vectorcardiographic measurements

2 Higher multipole terms improve the accuracy of the calculated potential field and correspond therefore, to a more accurate equivalent source representation.

3 Higher terms involve higher spatial harmonics the improvement produced by adding more terms is similar to that in the Fourier synthesis of periodic (temporal) signals.

What is of further importance in the multipole approach is that in principal a_{nm} and b_{nm} coefficients of equation (4) can always be determined by measurement at the body surface

†In this example the quadrupole (r^3 term and the r^5 term do not occur actually all odd inverse powers of are null (because of the symmetry even harmonics do not occur They correspond to the missing inverse odd powers of in equation (4).

REFERENCES

1 Brody D A, Bradshaw J C, and Evans, J W A theoretical basis for determining heart lead relationships of the equivalent cardiac generator I R E Trans. Bio. M. Elec BME 8 139 1961

2. Brody D A, and Bradshaw J C. The equivalent generator components of uniform double layers, Bull Math Bioph sics 24 183, 1962.

3 Geselowitz, D Multipole representation for an equivalent cardiac generator Proc. I. R. E. 48 75 1960

4. Hlavin, J M and Plonsey R An experimental determination of multipole representation of turtle heart, I. E. E. E. Trans. Bio. Med. Elec. BME 10:98, 1963

5. Stratton, J A. Electromagnetic theory New

York, 1943, McGraw Hill Book Company Inc.
6 Yeh, G K and Martinek, J Comparison of surface potentials due to several singularity representations of the human heart, Bull. Math. Biophysics 19:293 1957
7 Yeh, G K Martinek, J and de Beaumont, H Multipole representations of current generators in a volume conductor Bull. Math. Biophysics 20:203 1958.
8. Wilson, F N Johnston, F D Rosenbaum, F F and Barker P B On Einthoven's angle, the theory of unipolar electrocardiographic leads, and the interpretation of the precordial electrocardiogram, Am. Heart J. 32:277 1946.

Case reports

Incarceration of transvenous pacemaker electrode Removal by traction

Aydin M Bilgutay M.D
\ Kenneth Jensen M.D
*W Robert Schmidt M.D ****
*Joseph J Garamella M D ***
Michael F Lynch M.D
Minneapolis Minn

ac pacing by transvenous elec trode has extended this therapeutic odality to those too ill for thoracotomy hus, it is often temporarily used in rhythm isturbances due to myocardial infarction. ransvenous electrodes are also used ex ensively for permanent cardiac pacing voiding the hazards of thoracotomy re quired for epicardial electrodes.

The present development of demand im pulse generators, which avoid the risk of competition stimulation with resultant ven ricular arrhythmia and fibrillation will atly increase the usefulness of the trans- nous electrode particularly in the man nent of myocardial infarction Trans- enous pacing has been beset with many plications. While the improvement of mpulse generators promises to reduce their ated complications materially the prob- s of the transvenous electrodes remain hese complications are well documented the literature.[1-7]

The transvenous electrode is quickly in- corporated into the right ventricle wall st by mural thrombus formation which is soon converted to scar by fibroblastic in growth. The somewhat bulky one inch of flexible electrode† leading to the distal platinum tip is designed to minimize the risk of ventricular perforation and allows the electrode to be held firmly in this fibrous tissue. This is desirable as it prevents dis- placement of the electrode with loss of pacing However when the need for elec trode removal arises difficulties result from the fixation.

Case histories

Case 1 A 43-year-old man was admitted to St. Mary Hospital in Minneapolis, on Jan. 24 1967 following the onset of substernal crushing pain. Initial electrocardiogram (ECG) showed posterior myocardial infarction On the fourth day first degree and intermittent second degree heart block ppeared, progressing to intermittent complete heart block with entricular rate of 50 to 60 per minute. On the tenth hospital day the entricular rate dropped to 30 and intravenous Isuprel was required to maintain adequate cardiac output. A transvenous pacemaker was implanted and 20 days later the patient was discharged from the hospital with the pacemaker functioning. After 2 eeks, the impulse generator was turned off by

Received for publication Dec. 96
*Correspondent 1429 Medical Arts Building Minneapolis Minn 55402
**Clinical Associate Professor of Surgery University of Minnesota.
***Clinical Assistant Professor of Surgery University of Minnesota
†Medtronic Model No. 5810C.

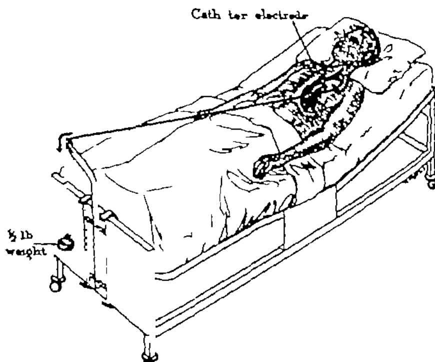


Fig 1 Diagram showing sustained traction applied for removal of incarcerated transvenous pacemaker electrode

percutaneous needling of the unit as sinus rhythm had returned He remained well and eturned to his home which was a distance of several hundred miles.

H ret rned 18 weeks after insertion nd remov l of the pacemaker was undertaken with local anesthesia. The impulse generator was removed from the nterior chest wall and the electrod was exposed where it entered the jugular eln. The electrode could not be pulled from the heart With heavy traction on the electrode the ECC would show either bradycardia or entricula tachycardia. It was lected t abandon removal of the entire electrode nd accordingly t was cut and the impulse generator removed from its pocket. Ten days later infection developed about the remaining electrode w th thrombosis of the left subclavia and jugular eins. Coagulase positive Staphylococ cus ureus bacteremia dev loped This was controlled with antibiotics, but the wound on the chest w ll remained purulent It was evident that the electrode should be removed. Hand traction of the electrode w gain nsuccessf l. Repeatedly the electrode could be pulled out of the ei nd stretched for a distance of 3 or 4 inches, but ventricular tachycardia would ensue. Upon release of the electrode it would retract back into the jugula vein for the entire distance it had been withdrawn. Removal of the electrode without incident was accomplished by sustained traction well below the pull that produced entricular arrhythmia This was accomplished by attaching the end of the electrode to a cord leading to half-pound weight suspended over pulley at the end of the bed (Fig 1) Removal was accomplished in the course of a few min tes.

Case 2 A 31 year-old woman was admitted to North Memorial Hospital in Minneapolis, on J 17 1967 with history of sudden onset of episodes of syncope The ECG showed complete heart block. A transvenous pacemaker electrode was inserted through the right saphenous vein and connected to n external pacemaker Extensive studies failed to show the etiology of heart block. Is her own ... never showed signs of returning to ... and because there was evidence of phlebitis developing in the right leg on J ly 27 1967 an epicardial fixed-rat pacemaker was implanted through thoracotomy Attempted removal of the transvenous electrode after surgery met ... distance nd it ppeared that the electrode was incarcerated in the ventricle and, or along ... in the inferior vena cava and saphenous ... tained traction by the same arrangement ... 1 pound weight wa ithout success after ... utes, but effective in a few minutes after ... the weight to 2 pounds.

Discussion

Review of the literature indicates ... under similar circumstances others have pulled the electrode out of the vein ... as it would come without ventricular ... culties then cut it off and let the remainder ...

the electrode retract into the vein They ve then resorted to cardiotomy to remove e remainder of the electrode [4,7] Gentle eady traction has been useful also for moval of electrode wires inserted in the ntricular wall at the time of cardiac sur ry It has been our experience that, not frequently such myocardial wires could t be completely removed and we have d to be content with pulling the electrode t as far as it would come and cutting it f at this point hoping the unrecovered rtion would not be troublesome

Summary

A transvenous electrode may become mely adherent to the endocardium of the ght ventricle and resist removal

Adherent electrodes have been removed y gentle steady traction in 2 such in-ances. This method may be worthy of ial before cardiotomy is undertaken to move an incarcerated electrode.

REFERENCES

1 Jensen N K., Schmidt, W R Garamella, J J Lynch, M F and Peterson, C. A. Intracavitary cardiac pacing J.A.M.A. 195:916, 1966.

2 Yuceoglu, Y Z., Lunger M and Dresdale, D T Transvenous electrical pacing of the heart. Results of 96 insertions in 78 patients, Am Heart J 1:5 1966.

3 Moss, A. J and Rivers, R. Myocardial perforation by permanent transvenous pacemaker New England J Med. 274:265 1966.

4 Rotem C. E., Greig, J H., and Walters, M B Air embolism to the pulmonary artery during insertion of transvenous endocardial pacemaker J Thoracic & Cardiovas Surg 53:562, 1967

5 Trevelyan, E. P Firmstone A. T and Leary J Endocardiac pacemaker induced diaphragmatic contractions, J A.M A. 200 1179 1967

6. Meckstroth, C. V Schoenfeld, C S., and Wardwell, G A. Myocardial perforation from a permanent endocardial electrode, J Thoracic & Cardiovas Surg 54 16, 1967

7 Danielson, G K Shabetai, R., and Bryant, L. R. Failure of endocardial pacemaker due to lat myocardial perforation, J Thoracic & Cardiovas. Surg 54:42 1967

Second degree heart block occurring in a patient with Prinzmetal's variant angina

Ronald E. Gillilan, M.D.
Richard R. Hawley, M.D.
J. Richard Warbasse, M.D.
Baltimore, Md.

Prinzmetal and co-workers have described a variant form of angina pectoris characterized by chest pain at rest accompanied by electrocardiographic S-T segment elevation. Approximately 50 per cent of patients with this form of angina have cardiac arrhythmias during attacks of chest pain. Ventricular arrhythmias including premature ventricular contractions, bigeminy, and paroxysmal ventricular tachycardia are mentioned by Prinzmetal as being the most frequent abnormalities in heart rhythm noted. The patient reported here demonstrates second degree heart block with periods of Wenckebach phenomenon during his episodes of chest pain. In our review of the literature, we have been unable to find a report of this particular type of arrhythmia occurring in association with this variant form of angina pectoris.

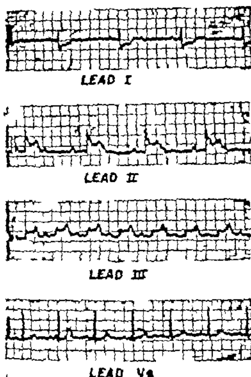
Report of a case

R. L., 56-year-old American seaman, was admitted to the Baltimore United States Public Health Service Hospital on April 27, 1967, because of intermittent chest pain of 5 days duration. On April 22, 1967, he began to have episodes of dull aching substernal chest pain with radiation into the elbows occurring while at rest and lasting only 2 or 3 minutes. Usually the pains occurred at approximately 7 A.M. while the patient was still in bed, and were not brought on by physical exertion at any time. He came to the outpatient dispensary because of daily recurrences of these pains.

His past history is significant in that he was well until Dec. 27, 1966, when he was admitted to another hospital because of chest pain. A diagnosis of acute anterior myocardial infarction was made during the admission and documented by serial electrocardiographic and serum enzyme changes. During the first several days of that hospitalization the patient had frequent premature atrial beats which subsided after the institution of digitalis and quinidine therapy. The remainder of his hospital course was uneventful. He was asymptomatic at the time of his return to work in April, 1967, and remained so until 5 days prior to the present hospital admission.

At the time of the present hospital admission the patient's blood pressure was 150/70 and his pulse was 88 per minute and regular. No significant abnormalities were noted on the physical examination. The electrocardiogram (ECG) shown in Fig. 1 was obtained during one of his brief episodes of chest pain on the day of admission to the hospital. During this mild episode of chest pain, there was second degree heart block in Leads I and II and S-T segment elevation in Leads II and III. The chest pain subsided spontaneously while the ECG in Fig. 1 was being obtained. Lead III, recorded immediately after Leads I and II, indicates that the severity of the arrhythmia had diminished to first degree heart block, although the S-T segment elevation persisted. The precordial leads, recorded immediately after the limb leads, demonstrate that the rhythm had returned to normal and no abnormal S-T force was seen. A repeat ECG taken 30 minutes later (Fig. 2) showed an old anteroseptal myocardial infarction and was unchanged from tracings taken in March, 1967.

From the United States Public Health Service Hospital, Baltimore, Md.
Received for publication Dec. 14, 1967.



1 ECG of the patient during a brief episode chest pain.

The patient as placed on bed rest and continued on digoxin 0.25 mg daily nitroglycerin 0.4 mg as needed for chest pain, and hydrochlorothiazide 50 mg daily. He continued to have daily episodes of chest pain lasting 2 to 3 minutes. Electrocardiographic monitoring was done with the Sanborn model 780 Viso-monitor with the chest electrodes *attached in such a manner as t obtain* record comparable to Lead II on the tandard ECG. During the episodes of chest pain, the patient ECG consistently showed S-T segment levation and second degree heart block, with return to normal sinus rhythm with isoelectric S-T segments as the pai ubsided. Occasionally Wenckebach phenomenon was observed during the chest pain, as show in Fig 3. The serum glutamic oxaloacetic transaminase serum lactic de h drogenase and white blood count were repeatedly within normal limits. By the tenth day of hospitalization the episodes of chest pain were very mild in intensity each lasting only about one minute. At these times, the ECG obtained during pain showed no heart block and less S-T segment elevation. After 29 day of hospitalization the patient was ormally active and without chest pain. He has continued his convalescence t home with gradual increase of his activities and has remained free of symptoms.

Discussion

This case demonstrates several of the features of variant angina pectoris as described by Prinzmetal and co-workers.

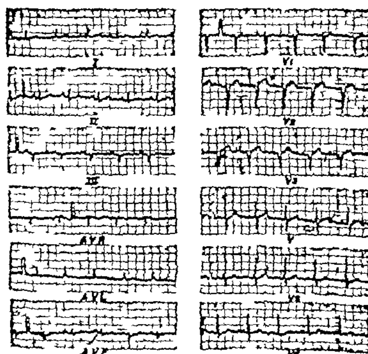


Fig. ECG obtained when the patient was pain free.

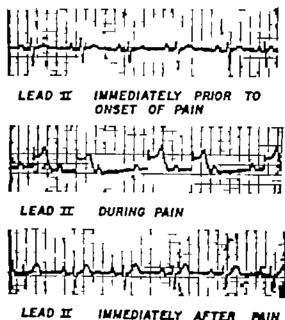


Fig 3 Lead II obtained from the cardiac monitor before dur ng nd after chest pain.

The nature of the patient s chest pain was similar to that seen in patients with classic angina pectoris but its occurrence during periods of inactivity is typical of the Prinzmetal s variant angina. Another feature of this entity is the tendency for the pain to occur at about the same time each day This patient s pain occurred most often at about 7 A.M shortly after he had awakened and had no apparent relation ship to meals or physical activity It has been stated that pain in this variant form of angina is frequently more severe and longer in duration than in classic angina However this patient s chest pain was only moderately severe and was brief in duration seldom lasting more than 3 minutes. The patient demonstrates the characteristic electrocardiographic feature of the Prinzmetal variant form of angina. Marked S-T segment elevation appeared transiently in Leads II and III while the patient was experiencing pain This differs from classic angina pectoris which gener ally shows S-T segment depression during chest pain.

Abnormalities in cardiac rhythm are not uncommon in patients with ische heart disease. Prinzmetal and co-w noted that about 50 per cent of the with variant angina had arrhythm during severe pain [2] Ventricular arr mias were most common in their exp ence, and have been noted by other servers also [3,4] Botti[4] described a pa who in 4 days had at least 14 tra episodes of first second and third de heart block associated with chest p Though an acute inferior posterio myocardial infarct was diagnosed Pri metal s variant angina may have occu Our patient developed second degree h block at times with Wenckebach ph nomenon while having his episodes of chest pain During the period of hos zation his symptoms improved wi development of a myocardial infarct Patients with an acute inferior myocard infarction are prone to develop he block because there is a common bl supply via the right coronary arter the inferior myocardium and the a ventricular node in 90 per cent of in viduals.[5] Thus, it is not surprising observe heart block in patients with paired right coronary artery circula of sufficient degree to produce angi but not infarction.

REFERENCES

1 Prinzmetal, M Kennamer R Merliss R Wada, T and Bor N Angina pectoris I A variant form of angina pectoris, Am J Med. 27:375 1959
2 Prinzmetal, M Ekmekci, A Kennamer, R Kwoczynski, J Sh bin, H and Toyoshima H Varia t form of angina pectoris. Pre ously undelineated syndrome J.A.M.A. 17 1794 1960.
3 Robinson J Prinzmetal' variant angi pectoris, AM HEA T J 70 797 1965
4 Botti, R. A ariant form of angina pec with recurrent transient complete heart bl Am. J Cardiol. 14 443 1966.
5 Courter S. Moff t J and Fowler N A vanced trioventricular block in acute m cardial infarction, Circulation 27 1034, 19
6. James, T : Arrhythmias and conduction d turbances i acut myocardial infarction A HEART J 64:416, 1962.

Metabolism of the heart in health and disease Part III*

Lionel H. Opie, M.D.
London, England

X. Pathological conditions

Congestive heart failure. The importance of the abnormalities described in the processes of oxidative phosphorylation, high energy compound metabolism, calcium metabolism, contractile proteins, protein synthesis, and catecholamine metabolism has already been evaluated. It is apparent that there is no general agreement on the abnormalities found, nor any unifying hypothesis to explain divergent reports. A basic finding that has not been fully appreciated is the distortion and destruction of sarcomere structure by undue stretching in congestive failure.[93] Extreme degrees of stretch must lead to spatial distortion with poor interaction between actin and myosin at the cross-bridges. The consequences could well include decreased ATPase activity,[94,95] decreased ...tility of isolated myofibrils,[93] decreased usage of high energy phosphates, and heart failure with a normal or near normal level of high energy phosphates.[95] Another possible result of mechanical distortion is the early occurrence of mitochondrial damage, which would explain decreased rates of oxidative phosphorylation and a shift from aerobic to anaerobic metabolism in terminal heart failure.[44,117] It would therefore be of major importance to study further the biophysical damage occurring in the contractile mechanism and in the mitochondria and to correlate such changes with biochemical lesions.

Thyrotoxic heart disease. The relation between thyrotoxicosis and heart failure is not simple. Some clinical studies suggest that thyrotoxicosis only causes heart failure when another co-existing cardiovascular disease is present, but the detailed studies of Sandler and Wilson[196] argue for pure thyrotoxic heart disease. They studied 462 thyrotoxic patients, of whom 150 had significant cardiac involvement. The existence of a thyrotoxic cardiomegaly was

From the M. R. C. Metabolic Reactions Research Unit, Department of Biochemistry, Imperial College, London, S. W. 7, England.

The following abbreviations have been used:

ATP	adenosine-5'-triphosphate	NADP and NADPH$_2$	= oxidized and reduced forms of nicotinamide-adenine dinucleotide phosphate (formerly TPN and TPNH$_2$)
ADP	adenosine-5'-diphosphate		
AMP	adenosine-5'-monophosphate		
Pi	inorganic phosphate		
Cyclic AMP	= cyclic adenosine-3',5'-monophosphate	FFA	free fatty acids or nonesterified fatty acids or nonesterified fatty acids (NEFA)
CP	= creatine phosphate or phosphocreatine	TGFA	= triglyceride fatty acids
NAD and NADH$_2$	oxidized and reduced forms of nicotinamide-adenine dinucleotide (formerly DPN and DPNH$_2$)	G-6-P	= glucose-6-phosphate

*Part I appeared in the November, 1968 issue and Part II appeared in the January, 1969 issue of this Journal.

shown in 13 patients with conspicuous left ventricular enlargement (proved radiologically and confirmed electrocardiographically) but occurring in the absence of atrial fibrillation congestive heart failure or other coincidental heart disease Such cardiomegaly did not respond to radioiodine treatment in contrast to the good response of those with atrial fibrillation and congestive failure Necropsy studies in 3 patients also showed that hypertrophy of one or both ventricles could result from thyrotoxic heart disease.

Summers and Surtees[illegible] also found generalized or left ventricular cardiomegaly solely due to thyrotoxicosis. The existence of pure thyrotoxic heart disease as suggested by Likoff and Levine [illegible] seems established and this conclusion is supported by the occurrence of cardiomegaly in hyperthyroid experimental animals.[374] However age and coexisting heart disease frequently contribute to the picture in man

Interaction with catecholamines has been thought to explain some features of thyrotoxic heart disease. Brewster and his co-workers[illegible] abolished tachycardia and hypertension in thyrotoxic dogs subjected to a high spinal anesthetic, and showed that hyperthyroidism sensitized the body to the effects of reflexly released or administered catecholamines. Norepinephrine most closely simulated the physiological effects of hyperthyroidism. However there are other reports that the cardiac response to norepinephrine in the dog is not affected by variations in the thyroid status.[illegible] Furthermore the velocity of shortening and the rate of tension development of isolated cat papillary muscle are much increased in muscles from hyperthyroid cats independent of the level of norepinephrine stores.[illegible] Another contradiction lies in the catecholamine level of the hyperthyroid animal heart in the guinea pig the level is up in the rat the level is down [447] while in the cat it is unchanged [illegible]

In man too the position is confused The tachycardia induced by large doses of triiodothyronine can be abolished by the simultaneous administration of a catecholamine antagonist guanethidine [illegible] On the other hand β-blockade by [illegible] duces no change in the cardiovasc patients with spontaneous thyrotoxic also the hemodynamic effects of c cholamine infusions are no differe euthyroid humans from those ren hyperthyroid by triiodothyronine.[illegible]

Both thyroid and catecholamines r lize FFA from adipose tissue and incre FFA utilization by the hyperthyroid he is associated with decreased glucose up and oxidation [illegible] These changes r accompanied by increased myocardial le of carnitine acylcarnitines, and car acyltransferase.[441] Such increased FFA u zation may contribute to the exce oxygen uptake of the thyrotoxic heart.

Thyroid hormone may also act on o tive phosphorylation. Thyrotoxic he have an increased concentration of m chondria, in which the process of oxid phosphorylation is less efficient.[illegible] may be because thyroxin can loose uncouple oxidative phosphorylation which would explain decreased ATP a CrP content of hearts from thyro rats and guinea pigs.[illegible] The degree of uncoupling is increased by calcium r and decreased by deviations of the m nesium concentration from the optimal [illegible] In man there is only very mi evidence for uncoupling consisting of release across the thyrotoxic hea

Other actions of thyroid hormones a molecular level include an effect on structure and stability of mitochon (perhaps localized to the mitochond membrane) altered oxidation rates of mitochondrial and extramitochondrial tems, and stimulation of RNA synthe Some of these actions, including that oxidative phosphorylation can onl elicited by very high concentrations thyroid hormones, probably greater th those found even in severe thyrotoxico Tata[illegible] suggests that physiological c centrations of thyroid hormones stimul metabolism by a general increase in cytoplasmic capacity to synthesize p tein which leads to increased activity respiratory enzymes. Hence the ph ological action is anabolic. In toxic c centrations, thyroid hormones cause coupling In contrast to this view

ling of Hoch[333] that the dose of thy ine required to alter mitochondrial piratory control is 60 to 75 times less n the dose of triiodothyronine which uences protein synthesis in hypothyroid s.

Yet another view relates the actions of roid hormones to increased enzyme ivities. An enzyme of the glycerol-P le, mitochondrial glycerol P oxidase increased in thyrotoxic heart tissue ich suggests an increased capacity for glycerol P cycle and therefore for colysis.[341,342] Because it has been sup- sed that there is a relatively minor role the glycerol P cycle in the heart (see ussion in Section VI) an increase of cerol-P oxidase activity is unlikely to an important metabolic factor in the nesis of thyrotoxic heart disease.

Vitamin deficiencies may contribute to yrotoxic heart disease Vitamins A C thiamine nicotinamide pyridoxine ntothenic acid and vitamin B_{12} are tentially or actually deficient in hyper yroidism.[31,343,333] Of these thiamine de iency is the best-documented and the ajority of patients with thyrotoxicosis ay have thiamine deficiency as revealed y decreased concentration of free thi mine and d phosphothiamine in blood The implication is that the heart disease f thiamine deficiency may complicate rotoxic heart disease

In summary it is convenient to think hat thyroid hormone has both sympa homimetic and molecular actions on the rt. The sympathomimetic effect causes ncreased rate and force of contraction and the latter may result from a direct ffect on the contractile mechanism How the existence of a sympathomimetic ffect does not necessarily mean that yroid hormone and catecholamines have ynergistic effects rather at present it ppears that their effects are additive[344] Molecular actions are both anabolic and atabolic. The anabolic effect stimulates protein synthesis, and this may underlie hyrotoxic cardiomegaly The occurrence of cardiomegaly would however probably depend on a complex interaction between the degree of thyrotoxicosis the rate of secretion of other anabolic hormones such as growth hormone and the load placed on the heart by the hyperdynamic circu lation The catabolic effect may cause uncoupled respiration which would be expected to contribute to heart failure

Myxedema heart disease Although the occurrence of a true myxedema heart disease has been questioned[333] the coexistence of a serum lactate dehydrogenase pattern indicating myocardial damage together with electrocardiographic and radiological abnormalities is strong evidence for this entity[334] Substrate metabolism of the myxedematous myocardium has been the subject of only a few studies In the hypothyroid dog there is bradycardia reduced coronary blood flow and a decreased left ventricular oxygen consumption.[333,335] In contrast a patient with hypothyroidism and Hashimoto's thyroiditis had normal values for cardiac output, coronary blood flow and myocardial oxygen consumption[336] However glucose uptake was enough to account for more than all the oxygen uptake perhaps suggesting storage of glucose as glycogen This would agree with the increase in cardiac glycogen found in thyroidectomized rats.[?]

The contractile mechanism may be altered in myxedema. Decreased contrac tility has been found in the isolated hearts from hypothyroid rats[337] and in papillary muscle from hypothyroid cats.[344] The con tractile response to added catecholamines is also held to be diminished[337] and the level of catecholamine in the hypothyroid guinea pig heart is decreased[?] However there are also several reports of normal catecholamine metabolism in the hypothyroid heart.[337,338] Thus, at present, the metabolism of the hypothyroid heart has not been sufficiently well characterized to present a clear picture If however it is accepted that thyroid hormone has a direct stimulatory effect on the contractile mechanism, then decreased con tractility would be expected in hypothyroidism

Acromegalic heart disease The development of giant hearts over 1 000 grams in weight stresses the possible extent of cardiac enlargement in acromegaly[339,340] However the average heart weight is 160 per cent above normal compared with 151

*Table V Myocardial metabolism in thiamine deficiency**

Substrate uptake per 100 gram/min	Acute beriberi†	Recovering beriberi‡	Normal*
Oxygen ml	3 9	7 4	[illegible]
Glucose, mg	0 6	6 7	[illegible]
Pyruvate mg	0	0 3	[illegible]
Lactate, mg	0 6	2 3	[illegible]
FFA, μEq	9 1	11 1	[illegible]
FFA oxygen extraction ratio	133%	84%	[illegible]

*Calculated from the data of Brink and associates[illegible]; Bing and co-workers[illegible]; and Table IV
†Patients fasting.
‡Patient postprandial

per cent for liver and kidney suggesting that in the average case of acromegaly the heart merely shares in the general splanchomegaly [illegible] Hypertension is more frequent than usual and is said to occur in the majority of patients with cardiomegaly The hypotension noted in some acromegalics may indicate past myocardial infarction or an advanced burnt out stage of the disease with hypopituitarism [illegible] Heart failure is favored by hypertension and the increased heart work following splanchnomegaly The evidence for the existence of acromegalic *cardiovascular* disease is, therefore good Radiologically demonstrable cardiomegaly and electrocardiographic damage can however occur in the absence of hypertension[illegible] suggesting the existence of a specific acromegalic cardiopathy To qualify for the diagnosis of acromegalic heart disease other coincident causes of cardiomegaly specifically need exclusion as in the 3 patients described by Bricaire and colleagues.[illegible] However such patients are rare and their myocardial metabolism is as yet unstudied

Beriberi heart disease Impaired pyruvate metabolism is not the sole cause of beriberi heart disease because such impairment also occurs in other situations such as diabetes mellitus and fasting[illegible] which are not associated with clinical signs of heart failure Furthermore myocardial pyruvate uptake is normal in dogs with experimental thiamine deficiency [illegible] while in man depressed uptake is evident only in severe beriberi (Table V) Depressed citrate cycle activity resulting from decreased α-oxoglutarate decarboxylation (another step requiring thiamine pyrophosphate) [illegible] explain the decreased myocardial [illegible] uptake of the beriberi heart (Table V However the extent of the depress[illegible] this decarboxylation in acute experim[illegible] beriberi may not be sufficient to [illegible] myocardial function [illegible] Other factors [illegible] cluding associated vitamin deficien[illegible] may also play a role [illegible] Catecholam[illegible] may accumulate in experimental thia[illegible] deficiency and have cardiotoxic effects Thus, the myocardial necrosis in exp[illegible] mental thiamine deficiency could be ca[illegible] cholamine-induced Yet another fa[illegible] contributing to beriberi failure might [illegible] leakage of enzymes from the hear[illegible]

Depressed carbohydrate metabolism [illegible] beriberi may be caused not only by th[illegible] mine lack, but by enhanced FFA oxid[illegible] (Table V) A vicious circle could be e[illegible] tablished whereby decreased carboh[illegible] drate usage results in increased FFA u[illegible] which in turn further decreases carboh[illegible] drate usage If for any reason FFA th[illegible] becomes unavailable to the heart, subse[illegible] deficiency could cause failure For th[illegible] reasons, studies of lipid metabolism [illegible] beriberi heart disease are indicated.

Alcoholic heart disease Evidence [illegible] accumulated in favor of a specific alcoho[illegible] myocardiopathy distinct from ber[illegible] or nutritional heart disease [illegible] [illegible] sistent and marked pathological cha[illegible] intramyocardial triglyceride accumulati[illegible] [illegible] Because the rate of utilizatio[illegible] ethanol by heart tissue is very low [illegible] the triglyceride accumulation cannot [illegible] sult from changes in the intracel[illegible] NAD/NADH₂ ratio as suggested for [illegible]

r A direct toxic effect of alcohol on conduction and contractile systems[103] ld explain mechanical deterioration of heart exposed to ethanol but does not ount for the accumulation of trigly ide

cess myocardial triglyceride can re t from (1) increased triglyceride syn *as from the uptake of circulating FFA* triglyceride fatty acid especially during ygen lack or utilization of alternate strates or from (2) increased trigly ide synthesis from non lipid sources h as glucose During an infusion of ohol into the dog at least part of the ocardial triglyceride accumulation re ts from a greatly increased uptake of culating triglyceride which occurs after ½ to 3½ hours[10] and it is consonant with tivation of clearing factor lipase by anol.[114] The other possibility of syn esis of myocardial triglyceride f om n-lipid precursors, has not been investi- ted

Other possible mechanisms of damage to e heart by ethanol include leakage of idative enzymes mitochondrial damage depressant effect of hyperosmolality myocardial function and alterations in ronary blood flow[10 144 90 448] In addition techolamine release may occu in acute coholism and account for some of the parent effects of ethanol Protein de ency in chronic alcoholism may also ntribute to impaired contractility

At present the simplest hypothesis for e metabolic effects of alcohol on the heart direct toxicity on the cell membrane llowing the uptake of fatty acids (derived circulating FFA or TGFA) to proceed t a rate exceeding their oxidation with subsequent accumulation of triglyceride ithin the heart. Alternatively activation f clearing factor lipase may be the stimu- us to increased uptake of TGFA.

Kwashiorkor heart disease The clinical eatures of heart disease in this form of antile protein malnutrition may be elated to a reduced muscle bulk as a con- sequence of protein deficiency [14]

Idiopathic and other myocardiopathies In idiopathic cardiopathy the arthat output is lecreased there is occasionally nhanced glycolysis and frequently en zymes such as malic dehydrogenase and aldolase are lost from the heart.[443] In idiopathic mural endomyocardiopathy as found in South Africa, substrate metabolism at rest has a normal oxidative pat tern but during exercise there is a tend ency for anaerobic metabolism as evi denced by an alteration in the redox state.[12] In obstructive cardiomyopathy there is also a tendency to lactate production and anaerobic metabolism by the heart, which may revert to normal after propanalol treatment.[10] Thus, the common theme to cardiopathies *is a tendency to an anaerobic* type of energy metabolism especially on exercise This is, of course, a rather non-specific finding

Diabetes mellitus The multiple metabolic abnormalities found in hearts from alloxan-diabetic rats include defects in glucose uptake, glycolysis glycogen metabolism glyceride synthesis and breakdown and protein synthesis (see previous sections) The question arises as to why a diabetic myocardiopathy has not been found in humans. One possibility is that it has not been searched for Another possibil ty is that alloxan-diabetes is a model of a very severe diabetic state complicated by marked ketosis and elevated circulating FFA levels such a state does not corre spond to the situation in most patients with diabetes mellitus. It seems probable that streptozotocin-diabetes is a better animal model of the diabetic state.[881]

Myocardial fibrosis Nutritional fibrosis has been produced in rats fed a maize diet wh ch is similar to that taken by Africans in South Africa in whom myocardiopathy can develop[186] Myocardial fibrosis also occurs in guinea pigs fed on a plantain diet which resembles that taken by Ugan dan Africans who develop endomyocardial fibrosis.[444] Both tryptophan deficiency and excess circulating 5 hydroxytryptamine have been implicated in the genesis of the myocardial fibrosis.[185 187] However cast iron evidence for these mechanisms is lacking at present

In *carcinoid heart disease* fibrosis in the form of ca cinoid plaques occurs especially on the valvula a eas of the right heart.[444] The exact elationship between excess circulating 5 hydroxytryptamine and the

valvular lesions is not clear. A prolonged serotonin infusion into the aorta of the dog produces fibrosis of the mitral, aortic, and tricuspid valves,[143] which is a distribution not found in carcinoid heart disease. It is also difficult to relate the positive inotropic effect of 5-hydroxytryptamine[144] to the cardiopathy. The similarity of the urinary loss of 5-hydroxyindole acetic acid in cardiac and non-cardiac cases of carcinoid disease suggests that factors other than excess 5-hydroxytryptamine may be involved.[144] The diversion of tryptophan from protein and nicotinic acid synthesis raises the possibility of nutritional heart disease. That a combination of causes may be responsible for carcinoid heart disease is suggested by the occurrence of endocardial and intimal fibrous proliferation in guinea pigs after a combination of hyperserotoninemia, tryptophan deficiency, and liver damage.[144] Hemodynamic factors may also contribute to the development of the fibrosis.[61]

Recent work has implicated the kinin peptides in the genesis of some of the clinical features of the carcinoid syndrome.[62] Kinins may play a part in carcinoid heart disease because they reduce peripheral vascular resistance and induce a high-output state.[144]

Other metabolic causes of cardiac fibrosis include severe alcoholic heart disease,[186] severe beriberi heart disease,[144] and isoproterenol induced myocardial necrosis.[31]

Myocardial infarction. Virtually all studies on experimental myocardial infarction have been carried out on the dog heart. Within 60 seconds of such infarction myocardial cells fail to contract.[187] As discussed in Section I, there is no obvious reason why the anoxic heart should stop beating so soon.

In the minutes immediately following experimental coronary occlusion by microspheres in dogs, there is myocardial output instead of uptake of glucose, pyruvate and lactate. This is associated with an acute reduction in coronary flow to the infarcted area, and probably reflects the effect of anaerobiosis in stimulating glycogen breakdown and glycolysis. Within minutes an experimentally infarcted area shows ultrastructural changes in that the myofibrils relax and particulate [illegible] decreases.[343] Within 1 to 2 hours [illegible] is an early swelling of mitochondria [illegible] the sarcoplasmic reticulum, followed [illegible] increased lipid droplets and [illegible]. Lipid formation in anoxic heart tissue [illegible] be related to increased tissue lipid [illegible]tion from exogenous FFA during [illegible]biosis[63,64] or from increased [illegible] associated with an increased NADH/NAD ratio.[88] The amount and rate of loss [illegible] myocardial K^+ is similar to the [illegible] Na^+ suggesting the replacement of [illegible]cellular K^+ by Na^+.[375] The K^+ loss [illegible] progressive and severe 24 hours [illegible] coronary occlusion in the dog, [illegible] per cent of the myocardial K^+ [illegible] K^+ is released into venous blood and the ensuing high K^+ may be associated [illegible] ectopic rhythms[373,374] especially in the first hour after the infarct.[376]

The infarcted area is almost [illegible]ately depleted of CrP and within 15 [illegible]utes ATP virtually disappears.[85] This [illegible] be in part related to altered oxidative phosphorylation in mitochondria [illegible] infarcted areas; such mitochondria [illegible] decreased consumption of inorganic phosphorous with depressed P/O ratios [illegible] in the one study the oxygen uptake [illegible] increased[378] whereas in the other[89] there was decreased oxygen uptake and [illegible] of ability to increase oxygen uptake [illegible] ADP addition.

The duration of anoxia required [illegible] produce irreversible damage appears [illegible] be in excess of 15 minutes[373,374] and probably about 30 to 60 minutes.[144] Over 60 [illegible]utes of oxygen-deprivation is required [illegible] depress Ca^{++} uptake by the sarcoplasmic reticulum.[144]

Catecholamines are lost from the [illegible]farcted tissue with 75 per cent disappearing within 24 hours.[379] There is, however, no direct evidence that catecholamines from this source cause the delayed ventricular tachycardias that [illegible] coronary ligation,[373,374] nor is there [illegible] cation for the routine use of β-blockade in the therapy of acute myocardial infarction.[379]

Within 4 hours of experimental [illegible]tion there is a fall in protein synthesis [illegible] measured by [14]C glycine incorpor[illegible]

.thin 3 to 4 days there are supranormal es of resynthesis, occurring first in the icleoli then in mitochondria, and lastly in microsomes. Incorporation into the itractile protein subcellular fraction re-mins subnormal, for at least 10 days[77] d the myocardial myosin content takes out one month to return to normal[77] The incorporation of C-glycine into otein of infarcted tissue is increased by atment with insulin growth hormone abolic steroids, and ascorbic acid these ents stimulate fibroblastic proliferation[198] It is assumed but not proved that stud es dog heart infarction are relevant to the uation in human myocardial infarction.

Therapy of myocardial infarction If a tassium chloride-glucose insulin (PGI) lution is infused into dogs before and ring the development of an experimental farction then mitochondria from the farcted area maintain normal oxidative osphorylation.[14] Similar treatment may iprove the mortality rate of patients after yocardial infarction[78,87] The mode of tion of the PGI regime is not clear In ogs with experimental infarction the tracoronary administration of procaine ride or PGI helps to prevent both K+ ss and ventricular arrhythmias.[140] Simi rly it is suggested that the PGI solution ay reduce the incidence of atrioven-ticular block in human myocardial in rction, by prevention of loss of intra ellular K+[87] Restoration of the myo-ardial K+ content may act either by maintenance of normal cardiac action potential,[141] or by restoration of the normal rates of oxidative phosphorylation.[14] It may be noted that K+ is required for optimal rates of respiration of isolated brain and liver mitochondria.[142,143]

Acidosis and myocardial infarction The acidosis associated with myocardial infarction may contribute to the high mor tality rates[144] Because a high pH is associated with increased phosphofructoki nase activity[41] and accelerated glycolysis in the isolated rat heart[41-43A] it appears to be theoretically desirable to induce alkalosis to achieve the maximal glycolytic rate to aid the survival of the anaerobic and infarcted tissues.[41]

Although the induction of alkalosis by Tris (THAM) accelerates glycolysis in rat heart slices it also depresses oxidative metabolism at pH 7 7 to 8 0 (Table VI) This does not contradict the finding of Delcher and Shipp[41] that a Tris buffer at pH 7 8 did not depress the oxidative metabolism of the isolated rat heart, because in their study the final pH of the buffer was only 7 5 If these results are at all applicable to the human heart, then correction of acidosis to normality or to mild alkalosis, rather than induction of severe alkalosis (pH exceeding 7 7) would be the aim during the use of Tris.

Conclusions

The topics that have been discussed include substrate utilization by the heart

able VI *Effect of pH and Tris buffer on glucose metabolism of rat heart slices*

nitial and final pH	6 8 (8)	7 1 (5)	7 4 (12)	7 7 (8)	8 0 (8)
Oxygen uptake, µl/Gm wet wt.	736 ± 45	790 ± 95	662 ± 56	520 ± 56	452 ± 71
Formation of					
$^{14}CO_2$	1 3 ± 0 1	1 6 ± 0 2	1 2 ± 0 1	0 9 ± 0 1	0 7 ± 0 1
lactate	3 2 ± 0 2	4 9 ± 0 8	6 2 ± 0 4	6 8 ± 0 3	8 0 ± 0 9
pyruvate	0 2 ± 0 01	0 2 ± 0 06	0 3 ± 0 04	0 5 ± 0 04	0 5 ± 0 01
Lactate/pyruvate ratio	21 ± 3	20 ± 3	19 ± 2	15 ± 1	16 ± 1

Glucose-U-^{14}C, 10 mM. Buffer contained Tris, 25 mM Ions (mEq./L.) N 140; K+ 5 1 Ca++ 5.5 Mg 2 6 Cl 148 SO − 2.6. $^{14}CO_2$, lactate and pyruvate formation expressed as µ moles glucose equivalent per gram et t./60 min. Unpublished data of Muller and Opie.

mitochondrial metabolism protein synthesis calcium and the contractile mechanism and the role of catecholamines. The metabolic changes found in various cardiopathies and in myocardial infarction are also reviewed

The importance of carbohydrate (glucose and lactate) as fuel for myocardial energy metabolism has recently been overlooked because studies in human and animal hearts selected conditions unduly favoring lipid utilization The control of glycolysis is much better understood than that of FFA oxidation In particular the points at which FFA oxidation inhibit glycolysis are well-defined and this has given rise to the concept that FFA oxidation normally restricts glycolysis while the rate of FFA oxidation is in turn controlled by the availability of fatty acid to the heart and hence by the circulating FFA concentration the latter is known to be influenced by the rate of lipolysis in adipose tissue This sequence makes the heart an organ devoid of intrinsic control of its substrate metabolism However the rate of FFA oxidation may be controlled within the heart by the carnitine system and by the availability of alternative substrates TGFA and ketone bodies are not important fuels for the human heart except perhaps in pathological conditions

As yet little is known about protein metabolism and the factors involved in the myocardial response to an increased work load The control of aminoacid uptake and protein synthesis by insulin and growth hormone may be directly relevant to the understanding of cardiac hypertrophy

ATP plays a prime role in the control of myocardial metabolism as emphasized by the importance of ATP in the contractile process and in maintaining ion gradients across cell and mitochondrial membranes ATP makes a major contribution to the control of glycolysis by inhibiting phosphofructokinase By yielding AMP and cyclic AMP during anoxia and catecholamine stimulation ATP indirectly activates phosphofructokinase and phosphorylase ATP probably also regulates the activity of the citrate cycle and hence the rate of oxidation of all myocardial substrates. Thus when ATP is [illegible] during the imposition of a work load [illegible] the heart there are compensatory [illegible] nisms for enhanced glycolysis and [illegible] strate oxidation

A second major regulator of myocard[illegible] metabolism is the calcium ion, which [illegible] participate in contraction either by [illegible] ing a chelating link between act[illegible] myosin or by overcoming the ATP [illegible] hibition of actomyosin contraction. F[illegible] tors governing the flux of calcium [illegible] across the cell and mitochondrial m[illegible] branes and in and out of the sarcopl[illegible] reticulum are therefore directly rel[illegible] to the control of cardiac contract[illegible]

A third major regulator of myoca[illegible] metabolism is catecholamine activity [illegible] is important in the regulation of ca[illegible] contractility The effect of catecholam[illegible] on glycogen breakdown and glycoly[illegible] well studied but probably not of pr[illegible] physiological significance when comp[illegible] with the effect of the contractile me[illegible] nism The level of cardiac catechola[illegible] is decreased in heart failure

In reviewing the metabolic abberr[illegible] in pathological states, it is apparent [illegible] no fundamental progress has been [illegible] in the understanding of congestive [illegible] failure However progress has been [illegible] toward the understanding of endo[illegible] and nutritional cardiopathies at a mo[illegible] lar level The metabolic changes in isch[illegible] heart disease are quite well defined, [illegible] it is not known which factors re[illegible] anaerobic glycolysis from maximal [illegible] which could perhaps contribute to [illegible] energy supply of the anoxic heart.

There are several theoretical argu[illegible] for the use of the potassium-glucose-[illegible] solution in myocardial infarction, but [illegible] clinical evaluation is still incomplete

It is noteworthy that many of the [illegible] advances have been made by stud[illegible] hearts of experimental animals as [illegible] hearts or subcellular preparations. It [illegible] be ideal to have methods of obt[illegible] human tissue for similar studies, but [illegible] are thus far few major species differe[illegible] apparent in the patterns of heart [illegible] [illegible] in heart and [illegible] It [illegible] therefore be anticipated that [illegible] vances will [illegible] further [illegible]

biochemical and biophysical techniques
animal models of human disease

I appreciate the support and encouragement of ofessor E. B. Chain, F.R.S. and the financial sistance of the British Heart Foundation and the ellcome Trust. The following criticized the manuscript: Dr Howard E. Morgan, Dr Joseph C. Shipp, Eric Newsholme, Dr Wieland Gevers, Professor J Brink, and M. K. R. L. Mansford. Sections re criticized by Dr D. S. Robinson and Dr Carl Hoang Dr Steven Mayer Professor A. Wollenerger and Professor W. Lochner provided manuscripts of papers in the press. The help of these lleagues has been invaluable.

REFERENCES

1. Bing, R. J. The metabolism of the heart Harvey Lect. 50:27 1954.
2. Bing, R. J. Cardiac metabolism, Physiol Rev 45:171 1965.
3. Stewart, J. T. M Kinney J J and Danforth, W. H. Metabolism of the normal and failing heart, Advances Int. Med 11:273 1962.
4. Evans, J R Editor Structure and function of heart muscle, Circulation Res. 15:(Suppl II) 1964
5. Cruickshank, E. W. H. Cardiac metabolism, Physiol Rev 16:597 1936.
6. Evans, C. L. The metabolism of cardiac muscle in Recent advances in physiology ed 6 London, 1939 J & A Churchill, Ltd p. 157
7. Locke F S., and Rosenheim, O. Contributions to the physiology of the isolated heart, J Physiol 36:205, 1907
8. Langendorff O. Untersuchungen am uberlebender Saugerthierherzen, Pfluger Arch Physiol. 61:291 1895
9. Knowlton, F P and Starling E H Experiments on the consumption of sugar in the normal and the diabetic heart J Physiol. 45:146, 1912.
10. Evans, C. L. The effect of glucose on the gaseous metabolism of the isolated mammalian heart, J Physiol. 47:407 1914
11. Cruickshank, F W H and McClure G. S. On the question of the utilization of amino-acids and fat by the mammalian heart, J Physiol. 86 1 1936.
12. Cruickshank, E. W H., and Kosterlitz, H W Utilization of fat by aglycaemic mammalian heart, J Physiol. 99:208, 1941
13. Lochner W and Hirche, H Kohlenhydratstoffwechsel bei Herzerkankungen, in Bartelheimer H., Heyde W and Thorn, W editors D-Glucose und verwandte Verbindungen in Medizin und Biologie, Stuttgart, 1966, Ferdinand Enke Verlag, p. 812.
14. Calva, E., Mujica, A., Bisteni, A and Sodi-Pallares, D Oxidative phosphorylation in cardiac infarct. Effect of glucose-KCl-insulin solution, Am J Physiol. 209:371 1965.
15. Randle P J and Morgan, H E. Regulation of glucose uptake by muscle Vitamins and hormones 20 199 1962.
16. Morgan H E., Neely J R., Brineaux, J P and Park, C R. Regulation of glucose transport, Chance, B Estabrook, R. W and Williamson, J R editors Control of energy metabolism, New York, 1965 Academic Press, Inc. p. 347
17. Morgan, H E Randle P J and Regen, D M Regulation of glucose uptake by muscle. 3 The effects of insulin, anoxia, salicylate and 2 4-dinitrophenol on membrane transport and intracellular phosphorylation of glucose in the isolated rat heart, Biochem. J 73:573 1959
18. Morgan, H. E., Henderson, M J Regen, D M and Park, C. R. Regulation of glucose uptake in muscle. I. The effects of insulin and anoxia on glucose transport and phosphorylation in the isolated, perfused heart of normal rats, J Biol. Chem 236:253 1961
19. Park, C. R Reinwein, D Henderson, M J Cadenas, E. and Morgan, H. E. The action of insulin on the transport of glucose through the cell membrane, Am. J Med. 26:674 1959
20. Fisher R B and Zachariah, P The mechanism of the uptake of sugars by the rat heart and the action of insulin on this mechanism J Physiol. 158 73 1961
21. Zachariah, P Contractility and sugar permeability in the perfused rat heart, J Physiol 158:59 1961
22. Mansford, K R L Influence of anti-insulin serum on glucose metabolism. II In the perfused heart, Diabetes 16:475, 1967
23. Williamson, J R Effects of insulin and diet on metabolism of L (+)-lactate and glucose by perfused rat heart, Biochem J 83:377 1962.
24. Neely J K Liebermeister H and Morgan, H E Effect of pressure development on membrane transport of glucose in isolated rat heart, Am J Physiol. 212:815, 1967
25. Morgan H E., Cadenas, E., Regen, D M and Park, C. R. Regulation of glucose uptake in muscle. II. Rate limiting steps and effects of insulin and anoxia in heart muscle from diabetic rats, J Biol. Chem. 236:262 1961
26. Randle P J Newsholme, E. A., and Garland, P B Regulation of glucose uptake by muscle 8. Effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes and starvation on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles, Biochem J 93:652, 1964
27. Newsholme, E. A., and Randle, P J Regulation of glucose uptake by muscle. 5. Effects of anoxia insulin, adrenaline, and prolonged starving on concentrations of hexose phosphates in isolated rat diaphragm and

perfused isolated heart, Biochem. J 80:655 1961

28. Crane, R. K. and Sols, A. A renal tissue hexokinases, Methods in Enzymology 1:277 1955.

29 England, P J., and Randle, P J Effectors of rat-heart hexokinases and the control of rates of glucose phosphorylation in the perfused rat heart, Biochem. J 105:907 1967

30. Regen D M D vis, W W Morgan H. E., and Park, C. R. The regulation of hexokinase and phosphofructokinase activity in heart m scle. Effects of allox diabetes, growth hormone, cortisol nd novin, J Biol. Chem 239:43 1964.

31 Karpatkin, S Helmreich, E. and Cori, C. F Regulation of glycolysis in muscle. II Effect of stim lation and epinephrine I solated frog sartorius muscle, J Biol Chem. 239:3139 1964

32 Newsholm E A and Randle, P J Regulation of glucose uptake by muscle. 7 Effects of f tty acids, ketone bodies and pyruvate nd of alloxan diabetes, starvation, hypophysectomy and adrenalectomy on the concentr tions of hexose phosphates, ucleotides nd inorganic phosphate in the perfused rat heart, Biochem. J 93:641 1964

33 Ørand, P Narahara, H T and Cori, C F Studies of tissue permeability VIII The effect of anaerobiosis on glucose uptake in frog sartorius muscle J Biol. Chem 237 3037 1962.

34 Danforth W H Helmreich, E. and Cori, C F The effect of contraction and of epinephrine on the phosphorylase activity of frog sartorius muscle, Proc. N t. Acad. Sc. 48 1191 1962

35 Kreisberg R A and Williamson, J R M tabolic effects of ouabain in the perfused rat heart, Am. J Physiol. 207:347 1964

36 Kreisberg, R A and Williamson, J R M tabolic effects of glucagon in the perfused rat heart, Am. J Physiol. 207 721 1964

37 M yer S. E., M yfield, A. C. and Haas, J A. Heart muscle hexokinase subcell lar distribution and inhibition by glucose-6-phosphate, Molec. Pharmacol. 2:393 1966.

38 Williamson, J R. Glycolytic control mechanisms. I Inhibition of glycolysis by acetate and pyruvate in the isolated perfused rat heart, J Biol. Chem. 240:2308, 1965.

39 Opie L. H Shipp, J C., Evans, J R., and Leboeuf B Metabolism of glucose-U-C^{14} in perfused rat heart Am. J Physiol. 203 839 1962.

40. Bing, R. J Siegel, A., Vitale, A., Balboni, F., Sparks, E., Taeschler M Klapper M and Edwards, S. Metabolic studies on the human heart in vivo. I Studies on carbohydrate metabolism of the human heart Am. J Med 15:284 1953.

41 Goodale W T and Hackel, D B: Myocardial carbohydrat metabolism in normal dogs, with effects of hyperglyce [illegible] starvation, Circulation Res. 1:[illegible]

42. Goodale W T Olson, R E and Hac[illegible] D B The effects of fasting and dia[illegible] mellitus on myocardial metabolism [illegible] Am. J Med. 27:212, 1959

43 Shipp, J C., Opie, L. H and Challo[illegible] Fatty acid nd glucose metabolism [illegible] perfused heart, Nature 189:[illegible]

44 Williamson, J R and Krebs, H A [illegible] acetate as fuel of respiration in the p[illegible] rat heart, Biochem. J 80:540, 1961

45. Danforth W H McKinney J. [illegible] Stewart, J T Transport and phosph[illegible] tion of glucose by the dog heart, J Phy[illegible] 162:367 1962.

46. M yer S. E. Action of epinephrine [illegible] cose ptake and glucose-6-phosphate [illegible] dog heart i situ Biochem. Pharm[illegible] 12 193 1963.

47 Newsholme, E. A., and Randle, P J [illegible] lation of glucose uptake by muscle [illegible] tose 1 6-diphosphatase activity of [illegible] and rat diaphragm, Biochem. J [illegible] 1962.

48. Opie, L. H., and Newsholme, E. A.: [illegible] activities of fructose 1,6 diphospha[illegible] phosphofructokinase and phosphoenolpyr[illegible] vate carboxykinase in [illegible] muscle [illegible] muscle, Biochem. J 103:391 1967

49 Mansour T E. Studies on heart phos[illegible] fructokinase purification, inhibition [illegible] activation, J Biol. Chem. 238:22[illegible]

50 Passonneau J V and Lowry [illegible] kinase and the control of citric acid [illegible] Biochem. Biophys. Res. Commun. 1[illegible] 1963

51 Opie L. H Effect of extracellular p[illegible] function nd metabolism of isolated [illegible] fused rat heart, Am. J Physiol. 20[illegible] 1965

52 Delcher H K and Shipp, J C. Eff[illegible] pH pCO and bicarbonate on metabol[illegible] glucose by perfused rat heart, Bi[illegible] Biophys. Acta 121:250, 1966.

52A Scheuer J and Berry M N: Effe[illegible] alkalosis on glycolysis in the isolated [illegible] heart, Am. J Physiol. 213:1143, [illegible]

53 Pogson, C. I., and Randle P J: The [illegible] trol of rat-heart phosphofructokinase [illegible] citrate and other regulators, Biochem [illegible] 100:683 1966.

54 Danforth, W H Activation of glycoly[illegible] pathways in muscle, i Chance, B [illegible] brook, R. and Williamson, J R [illegible] Control of energy metabolism, New York 1965 Academic Press, Inc., p 287

55. Ui, M A role of phosphofructokinase [illegible] pH-dependent regulation of glycolysis, Bio[illegible] chim. Biophys. Acta 124:310, 1966

56. Bücher T., and Rüssmann, W Equilibrium and nonequilibrium in the glycolysis [illegible] Angew Chem. Int. Ed. 3:426, 1964

57 Williamson, J R. Metabolic control in the [illegible] perfused rat heart, in Chance B [illegible]

brook, R. W and Williamson, J R editors Control of energy metabolism New York, 1965, Academic Press, Inc. p. 333

8. Ito, Y Studies on the myocardial metabolism of diabetes mellitus and the effects of insulin, glucocorticoid and epinephrine on the metabolism of the heart J p Circ. J 26 15, 1962.

9 Shipp, J. C., Delcher H K and Crevasse, L. E. Glucose metabolism by the hexose monophosph te pathway in the perfused rat heart, Biochim Biophys Acta 86:399 1964

0 Crevasse, L. E., Shipp, J C., and Delcher H K. Glucose metabolism by the hexose monophosphate pathway in heart-muscle homogenates, Biochim. Biophys Acta 86 402, 1964

1 Glock, G E., and M Lean, P Levels of enzymes of the direct oxidative pathw y of carbohydrate metabolism in mammalian tissues and tumours Biochem. J 56 171 1954

12. Glock, G. E., and M Lean, P Levels of oxidized and reduced diphosphopyridine nucleotide and triphosphopyridine nucleotide in animal tissues, Biochem. J 61:388, 1955

13. Jolley R L Cheldelin, V H and New burgh, R. W Glucose catabolism in fetal and ad lt heart, J Biol. Chem 233 1289 1958.

64 Coffey R G Cheldelin, V H. nd New burgh, R. W Glucose utilization by chick embry heart homogenates, *J Gen Physiol* 48 105, 1964

65 Gudbjarnason, S Cowan, C and Bing R. J Increase in hexosemonophosphate shunt activity during tissue repair Lif Sc. 6 1093 1967

66 Negamo, M and Hochrein H Störungen im Myokard bei Belastung und Insuffi zienz des Herzens, Klin Wchnschr 41 792 1963.

67 Garland, P B Some kinetic properties of pig-heart oxoglutarate dehydrogenase that provide basis for metabolic control of the enzyme activity and also stoichiometric assay for coenzyme A in tissue extract Biochem J 92 10c, 1964

168. Scriba, P and Holzer H Gewinnung von α-hydroxyäthyl-2 thiaminpyrophosphat ort Pyruvatoxydase aus Schweineherzmuskel, Biochem. Ztschr 334:473 1961

69 Garland, P B and Randle P J Control of pyruvate dehydrogenase in the perfused at heart by the intracellular oncentration of acetyl coenzyme A, Biochem. J 91:6c 1964

70. Evans, J R., Opie, L H and Renold, A. E Pyruv te metabolism in the perfused rat heart, Am. J Physiol. 205:971 1963

71. Wilson, A. C Cahn, R D and Kaplan N O Functions of the t forms of lactic dehydrogenase in the breast muscle of bird Nature 197:331 1963

72. Kaplan, N O nd Goodfriend, T L Role of the t t pes of lactic dehydrogenases, Advances Enzym Regulat. 2:203 1964

73 Vewell, E. S., and Pool, P E. Lactate and pyruvat in exercised, ischemic canine muscle relationship of tissue substrate level t lactate dehydrogenase, Proc. N t. Acad. Sc 56 756 1966.

74 Huckabee W E. Relationships of pyruvate and lactate during anaerobic metabolism I Effects of infusion of pyruvate or glucose and of hyperventilation, J Clin. Invest. 37:244 1958

75 Huckabee, W E. Relationship of pyruvate nd lactat during anaerobic metabolism V Coronary adequacy Am. J Physiol. 200 1169 1961

76 Gudbjarnason, S and Bing R J The redox-potential of the lactate-pyruvate system in blood as an indicator of the functional state of cellular oxidation, Biochim Biophys. Acta 60 158 1962

77 Olson, R. E. Excess lactate and anaerobiosis, An Int Med. 59:960 1963

78 Scheuer J Myocardial metabolism cardiac hypoxia, Am. J Cardiol. 19:385 1967

79 Glavuno, V V Distribution and gradient of lactate between blood and heart muscle, P oc Soc Exper Biol & Med. 118 1155 1965

80 Garland, P B Newsholme, E A., and Randle, P J Regulation of glucose uptake by muscle 9 Effects of f tty acids and ketone bodies, and of alloxan-diabetes and starvation on pyruv te metabolism and on lactate/pyruvate and L-glycerol 3-phosphate/dih droxyacetone phosphate concen tration ratios in rat heart and rat diaphragm muscles Biochem. J 93:665 1964.

81 Regan, T J Moschos, C B Lahan, P H Oldewurtel, H A and H llems, H K. Lipid and carbohydrate metabolism of myocardium during the biphasic inotropic re sponse to epinephrine, Circulation Res. 19:307 1966

82 Keul J Krause, H Overbeck, W Doll, E and Fleer U Uber den Stoff echsel des schlagenden, Keine Druck und Volumenar beit leistenden menschlichen Herzens I Klin Wchnschr 12:690 1964.

83 F ans, J R Cellular transport of long chain fatty acid Canad J Biochem 4 :955 1964

84 Scheuer J and Brachfeld, N Myocardial uptak and f actional distribution of palmitate-1-C[14] by the ischemic dog heart, M tabolism 15:945 1966.

85 Opie, L H Evans, J R and Shipp, J C Effect of fasting on glucose and palm tate metabolism by perfused rat heart, Am J Ph siol. 205 1203 1963

86. Ungar I Gilbert, N Siegel, A Blain, J M and Bing, R. J Studies on myocardial metabolism. IV Myocardial metabolism in diabetes, Am J Med 18:385 1955

87 Keul, J Doll, F Steim, H Homburger

H Kern, H and Reindell, H Über den Stoffwechsel des menschlichen Herzens. I Die Substratversorgung des gesunden men schlichen Herzens Ruhe, wahrend und nach körperlicher Arbeit Pflugers Arch. Physiol 282 1 1965
88. Lundsgaard Hansen, P Regional differences of the lactate/pyruvate response to progressive arterial hypoxemia Pflügers Arch Physiol. 292:60 1966.
89 Bretschneider H J Frank, A., Kanzow E. and Bernard I Uber den kritischen Wert nd die physiologische Abhängigkeit der Sauerstoff Sattigung des venösen Coronarblutes, Pflugers Arch 261:399 1957
90. Regan T J Koroxenidis, G. Moschos, C B Oldewurtel, H A Lehan P H and Hellems, H K The acut metabolic and hemodynamic responses of the left ventricle to ethanol J Clin. I vest 45:270 1966
91 Brink A J nd Lewis, C M Coronary blood flow energ tics, and myocardial metabolism i idiopathic m ral endomyocardiopathy (14 patients) Am. Heart J 73:339 1967
92 Gorl n, R Pathoph siology of cardiac pain, Circ lation 22 138, 1965
93 Herman M V Elliott W C and Gorlin R lectrocardiographic, anatomic and metabolic tud of onal myocardial ischemia m coronary heart disease, Circulation 35:834 1967
94 Scheuer J and Brachfeld N Coronary insufficiency relation between hemodynamic lectrical and biochemical parameters, Circulation Res. 18 178, 1966.
95 Brink A J Lewis, C. M and va Heerden P D R Coronary blood flow and myocardial energy met bolism in obstructive cardiomyopathy Am. J Cardiol. 19:548, 1967
96 Lochner W Mercker H and Nasser W Über den anaeroben Energiegewin des W rmblüterherzens in sit unter Cyanid vergiftung Arch. E per P th. Pharmakol. 236:365 1959
97 Danforth W H N egle S. nd Bing, R J Effect of ischemia and reoxygenation on glycolytic reaction nd adenosinetriphosphate m heart muscle Circulation Res. 8:963 1960
98 Cornblath, M R ndle, I J Parmeggiani, A and Morgan H E Regulation of glycogenoly is n muscle Effect of glucagon and anoxia on lactat production, glycogen content, and phosphorylase activity in the isolated perfused rat heart J Biol. Chem. 238 1592, 1963
99 Muller E. R Über die aerobe nd anaerobe Stoffwechselkapaz tät des isolierten Warmblüterherzens Pflügers Arch Physiol 276 42, 1962
100 Ballinger W F and Vollen eder H Anaerobic metabolism of heart Circulation Res. 11:681 1962.
101 Winbury M M I fluence f glucose on contractile activity of papillary muscle during and after anoxia, Am. J Physiol [illegible] 135 1956.
102. Winbury M M Experimental [illegible] to the development of antianginal [illegible] Advances Pharmacol. 3 1 1964
103 Yang, W C. Anaerobic functional [illegible] of isolated rabbit atria, Am. J Ph[illegible] 205:781 1963.
104 Wollenberger A., and Krause, E G [illegible] vation of α-glucan phosphorylase and [illegible] lated metabolic changes in dog [illegible] following arrest of blood flow [illegible] Biophys. Acta 6 :337 1963
105 Shonk, C. E. Koven, B. J Majima, [illegible] and Boxer G. E. Enzyme pattern in [illegible] man tissues. II Glycolytic enzyme patterns in nonmalignant human tissues, Cancer Res. 24 722 1964
106 Pogson, C. I and Randle, P J Effect of alloxan-diabetes, starvation and [illegible] physectomy on total phosphofructokinase activity in rat heart, Nature 212 [illegible]
107 Neill, W A Krasnow N Levine, [illegible] nd Gorlin R. Myocardial anaerobic metabolism in intact dogs, Am J Physiol 204:427 1963.
108. Clark, A. J Gaddie R., and Stewart, C P The anaerobic activity of the isolated frog heart J Physiol. 75:321 1932.
109 Dehaan, R L., and Field, J: Mechanism of cardiac damage in anoxia, Am J Physiol 197:449 1959
110 Crowell, J W and Kaufmann, B [illegible] Changes in tissue pH after circulatory arrest, Am. J Physiol. 200 743, 1961
111 Trivedi, B and Danforth, W H: Effect of pH on the kinetics of frog muscle phosphofructokinase, J Biol. Chem. 241:4110, [illegible]
112. Barboriak, J J and Hardman, H F [illegible] effect of pH on glycogenolysis in [illegible] heart, Biochem Pharmacol. 15 [illegible]
113 Kirk, E S. and Honig, C. E. [illegible] distribution of blood flow and gradients of oxygen tension with the heart, Am J Physiol. 207:661 1964
114 Leunissen R L.A Piatnek Leunissen, D [illegible] Nakamura, Y K and Griggs, D M [illegible] Regional distribution of the heart [illegible] educed coronary flow (Abstract), Circulation (Suppl. III) 31:115 1964.
114A. Lundsgaard Hansen, P Meyer C, [illegible] Riedwyl, H: Transmural gradients of [illegible] colytic enzyme activities in left ventricular myocardium Pflügers Arch. Physiol [illegible] 1967
115. Meerson F Z Compensatory hyperfunction nd insufficiency of the heart, Circulation Res. 10:250, 1962.
116 Lochner A., Opie, L. H and Brink, A J Defective oxidative phosphorylation in hereditary myocardiopathy in the Syrian hamster Cardiovasc Res. I press
117 Gudbjarnason, S de Schryver C M G nd Bing R J: Changes in myocardial enzyme pattern in human heart [illegible] J Lab & Clin. Med. 61 796, 1963

118. Blain, J. M., Schafer, H., Siegel, A. L., and Bing, R. J.: Studies on myocardial metabolism. VI. Myocardial metabolism in congestive heart failure, Am. J. Med. 20:820, 1956.
119. Lorber, V.: Energy metabolism of the completely isolated mammalian heart in failure, Circulation Res. 1:298, 1953.
120. Rowe, G. G., Afonso, S., Castillo, C. A., Lowe, W. C., and Crumpton, C. W.: The systemic and coronary hemodynamic effects of intravenous administration of 50% glucose, Am. J. M. Sc. 244:186, 1962.
121. Neptune, E. M., Jr., Foreman, D. R., and Reish, J. J., Jr.: A requirement for glucose by excised working rat diaphragm, Am. J. Physiol. 199:1048, 1960.
122. Gimeno, A. L., Gimeno, M. F., Savino, E. A., and Bedners, A. S.: Effects of glucose, pyruvate, lactate and starvation on contractility of isolated rat atria, Proc. Soc. Exper. Biol. & Med. 123:875, 1966.
123. Nakamura, K., Saunders, P. R., Webb, J. L., Lanson, H. C., and Thienes, C. H.: Metabolism of the heart in relation to drug action. IV. Effects of various substrates upon the isolated perfused rat heart, Am. J. Physiol. 158:269, 1949.
124. Krebs, H. A., and Woodford, M.: Fructose 1,6-diphosphatase in striated muscle, Biochem. J. 94:436, 1965.
125. Jedeikin, L. A.: Cardiac glycogen metabolism in vivo in fed and fasted rats (Abstract), Biochem. J. 99:6P, 1966.
126. Evans, G.: The glycogen content of the rat heart, J. Physiol. 82:468, 1934.
127. Lackey, R. W., Bunde, C. A., and Harris, L. C.: The relationship of cardiac glycogen deposition to blood ketone levels in experimental ketosis, Am. J. Physiol. 145:470, 1946.
128. Willebrands, A. F.: Over het verbruik van zuurstof en substraten door de zoogdier hartspier, Academic Thesis, University of Amsterdam, 1966.
129. Russell, J. A., and Bloom, W. L.: Hormonal control of glycogen in the heart and other tissues in rats, Endocrinology 58:83, 1956.
130. Lukens, F. D. W.: Influence of insulin on protein metabolism and cardiac glycogen in Houssay animals, Am. J. Physiol. 192:485, 1958.
131. Bowman, R. H.: Cardiac glycogen in hypophysectomized rats subjected to fatty acid feeding, Am. J. Physiol. 197:1017, 1959.
132. Blount, D. H.: Influence of restricted food intake on cardiac glycogen mobility, Proc. Soc. Exper. Biol. & Med. 122:148, 1966.
133. Leloir, L. F., Olavarria, J. M., Goldemberg, S. H., and Carminatti, H.: Biosynthesis of glycogen from uridine diphosphate glucose, Arch. Biochem. Biophys. 81:508, 1959.
134. Meyer, D. K., and Purdy, A. F.: Cardiac glycogen of rats during and following acute anoxia, Am. J. Physiol. 200:860, 1961.
135. Sövik, O., Oye, I., and Rosell-Perez, M.: The effect of anoxia, 2,4-dinitrophenol and 2-deoxyglucose on muscle glycogen synthetase, Biochim. Biophys. Acta 124:26, 1966.
136. Ozand, P., and Narahara, H. T.: Regulation of glycolysis in muscle. III. Influence of insulin, epinephrine and contraction on phosphofructokinase activity in frog skeletal muscle, J. Biol. Chem. 239:3146, 1964.
137. Kraupp, O., Adler-Kastner, L., Niessner, H., and Plank, B.: The effects of starvation and of acute and chronic alloxan diabetes on myocardial substrate levels and on liver glycogen in the rat in vivo, Europ. J. Biochem. 2:197, 1967.
138. Williams, D. J., and Mayer, S. E.: Hormonal effects on glycogen metabolism in the rat heart in situ, Molec. Pharmacol. 2:454, 1966.
139. Danforth, W. H.: Glycogen synthetase activity in skeletal muscle. Interconversion of two forms and control of glycogen synthesis, J. Biol. Chem. 240:588, 1965.
140. Beloff-Chain, A., Betto, P., Catanzaro, R., Chain, E. B., Longinotti, L., Masi, I., and Pocchiari, F.: The metabolism of glucose 1-phosphate and glucose 6-phosphate and their influence on the metabolism of glucose in rat-diaphragm muscle, Biochem. J. 91:620, 1964.
140A. Hers, H. G.: α-Glucosidase deficiency in generalized glycogen-storage disease (Pompe disease), Biochem. J. 86:11, 1963.
141. Jedeikin, L. A.: Regional distribution of glycogen and phosphorylase in the ventricles of the heart, Circulation Res. 14:202, 1964.
142. Dhalla, N. S., Haugaard, N., and Hess, M. E.: Cardiac phosphorylase in different species and after reserpine administration, Proc. Soc. Exper. Biol. & Med. 119:1147, 1965.
143. Krebs, E. G., Gonzalez, C., Posner, J. B., Love, D. S., Bratvold, G. E., and Fisher, E. H.: Interconversion reactions of muscle phosphorylases b and a, *in* Whelan, W. J., and Cameron, M. P., editors: Control of glycogen metabolism, London, 1964, J. & A. Churchill, Ltd., p. 200.
144. Robison, G. A., Butcher, R. W., Oye, I., Morgan, H. E., and Sutherland, E. W.: The effect of epinephrine on adenosine 3',5'-phosphate levels in the isolated perfused rat heart, Molec. Pharmacol. 1:168, 1965.
145. Sutherland, E. W., Øye, I., and Butcher, R. W.: The action of epinephrine and the role of the adenyl cyclase system in hormone action, Recent Progr. Hormone Res. 21:623, 1965.
146. Murad, F., Chi, Y. M., Rall, T. W., and Sutherland, E. W.: Adenyl cyclase. III. The effect of catecholamines and choline esters on the formation of adenosine 3',5'-phosphate by preparations from cardiac muscle and liver, J. Biol. Chem. 237:1233, 1962.
147. Butcher, R. W., and Sutherland, E. W.: Adenosine 3',5'-phosphate in biological materials. I. Purification and properties of

cyclic 3 ,5 ucleotide phosphodiesterase and use of this enzyme t characterize adenosine 3 ,5 phosphate in human urine J Biol. Chem 237 1241 1962

148 Wollenberger A Endogenous catecholamine mobilization and the shift to anaerobic metabolism in the acutely ischaemic myocardium in Symposium on the coronary circ lation d energetics of the myocar dium Mila 1966, Basel New York 1967 S. Karger p 200

149 Hornbrook, K P Quinn P A Stegel, J H nd Brod T M Thyroid hormone reg lation of ardiac glycogen metabolism, Biochem Pharmacol 14:925 1965

150 Drummond, C I and Duncan, L The action of calcium ion on cardiac phosphory lase b kinase J Biol Chem 241:3097 1966.

151 Morga H E nd Parmeggiani A Regulation of gl ogenol sis in muscle Whelan W J and Cameron M P editors Control of gl ogen metabolism London 1964 J & A. Churchill Ltd p 254.

152 Morgan, H E and Parmeggiani, A Regulation of gl ogenoly is in muscle III Control of muscle glycogen phosphorylase act t J Biol Chem. 239:2440, 1964

153 Newsholme E A Regulation of enzyme act vity Sci Progr 53:237 1965

154 Oy l The ole of phosphorylase a and b for the ontr l of glycogenolysis in the iso l ted workin rat heart, Acta physiol. scand d na 70:229 1967

155 Williamson J R Kinetic studies of epinephrine effects in the perf sed rat heart, Pharmacol Rev 18:205 1966.

156 Bloom W L nd Russell, J A. Effects of epinephrine nd norepinephrine on carbo h drate metabolism in the rat, Am J Physiol 183:356, 1955

157 M yer S E Williams, B J and Smith J M Adrenergic mechanisms in cardiac glycogen metabolism A n New York Acad. Sc 139:686, 1967

158 H ng F nd Larner J On the effect of adenosine 3 5 cyclophosphate on the kinase of UDPG:α-1 4-gluca α-4-glucosyl transferase, Biochem Biophys Res Commun. 23:259 1966.

159 Ribeiluma, J Wendt, V E Ramos, H Gudbjarnason, S Bruce T A nd Bing, R. J The effects of orepinephrine on the hemod namics and myocardial metabolism of normal human subjects, Am Heart J 67:672, 1964.

160. Blou t D H and Meyer D K Effect of cardiac work on glycogen f actions of the heart, Am J Phy iol 19 1013 1959

161 Shefley W B Code C F nd Visscher W B The nfluence of thyroid dinitrophe ol and swimming on th glycogen and phosphocreatine les l of the rat heart i rel tion to ardiac hypertrophy Am J Physiol. 138:652, 1943

162. Reeves, R. B Control of glycogen utiliza tion and glucose uptak in the anaerobic turtle heart, Am J Physiol. 205:23 1963

163 Hazelwood, R. L., and Ulrich, R. C Glycogen mobilization and ort in th heart Am. J Physiol. 200:999, 1961.

164 Olson, R E and Hoeschen, R J E genous lipid utilization by the h perfused rat heart, Biochem. J 105 1967

165. Denton, R. M and Randle, P J Concentration of glycerides and phospholipids rat heart and gastrocnemius muscle Effect of alloxan-diabetes and perfusion, Biochem J 104:416 1967

166 Neely J R., Bowman, R. H and M H E. Conservation of glycogen in the perfused rat heart developing intraventric pressure i Symposium of 4th meeting Federation of European Biochemical Societies Oslo, 1967 Universitetsforlaget,

167 Jedeikin, L. A., and Buckley N M G cogen concentration in orking and no working ventricles of isolated dog hearts Circulation Res. 20:463, 1967

168 Weisberg J and Robbard, S : Distrib of glycoge m rat heart, Am. J Ph 193:466 1938.

169 Saidrasulov S. S New data concer histochemical structure of the myocard Nature 200:275 1963.

170. Ballard, F B Danforth W H S and Bing, R. J Myocardial metab of fatty acids, J Clin. Invest. 39:711, 19

171 Carlsten, A Hallgren, B Jagenburg R Svanborg A and Werkö, L: Myocardi met bolism of glucose, lactic acid, am acids and fatty acids in healthy hum dividuals at rest and at different work l Scandinav J Clin. & Lab Invest. 13:41 1961

172. Scott J C., Finkelstein, L. J and Spi J J Myocardial removal of free fatty acids under normal and pathological cond Am. J Physiol 203:482 1962.

173. Evans, J R Opie, L. H and Shipp, J C Metabolism of palmitic acid in perfused r heart, Am. J Physiol. 205 766, 1963

174. Willebrands, A. F Utilization of esterif non-esterified fatty acids by the isol perfused rat heart, Biochim. Bioph 84:607 1964

175 Carlsten A., Hallgren, B Jagenburg R. Svanborg A and Werkö, L: Myocard arteriovenous differences of individual fatty acid in healthy human ind Metabolism 12 1063 1963.

176. Gordon, R. S Jr and Cherkes, A. U terified fatty acid in human blood pl J Clin. In est. 35:206 1956

177 Goodman, D S The interact of h erythrocytes ith sodium palmitate J Clin Invest 37 1729 1958.

178. Goodman, D S. The interaction of h serum lbumin with long-chain fat anions, J Am Chem Soc 80 ... 19

179 Fritz, I B and Kaplan E. The prese alt of carnitine action on palmitate m tabolism by heart muscle in Peeters E editor Protides of the biological f

Amsterdam, 1960, Elsevier Publishing Co., p. 252.
180. Opie, L. H., and Walfish, P. G.: Plasma free fatty acid concentrations in obesity, New England J. Med. 268:757, 1963.
181. Hales, C. N., and Randle, P. J.: Effects of low-carbohydrate diet and diabetes mellitus on plasma concentrations of glucose, non-esterified fatty acid, and insulin during oral glucose-tolerance tests, Lancet 1:790, 1963.
182. Rothlin, M. E., and Bing, R. J.: Extraction and release of individual free fatty acids by the heart and fat depots, J. Clin. Invest. 40:1380, 1961.
183. Harris, P., Chlouverakis, C., Gloster, J., and Jones, J. H.: Arteriovenous differences in the composition of plasma free fatty acids in various regions of the body, Clin. Sc. 23:113, 1962.
184. Willebrands, A. F.: Myocardial extraction of individual non-esterified fatty acids, esterified fatty acids and aceto-acetate in the fasting human, Clin. Chim. Acta 10:435, 1964.
185. Stein, O., and Stein, Y.: Metabolism of fatty acids in the isolated perfused rat heart, Biochim. Biophys. Acta 70:517, 1963.
186. Enser, M. B., Kunz, F., Borensztajn, J., Opie, L. H., and Robinson, D. S.: Metabolism of triglyceride fatty acids by perfused rat heart, Biochem. J. 104:306, 1967.
187. Rosetti, M., Vaidoli, O., Colombi, L., and Barbaresi, F.: Myocardial lipids after intense muscular work, Cardiologia 45:269, 1954.
188. Challoner, D. R., and Steinberg, D.: The effect of free fatty acid on the oxygen consumption of the perfused rat heart, Am. J. Physiol. 210:280, 1966.
189. Skipp, J. C., Thomas, J. M., and Crevasse, L.: Oxidation of carbon-14-labeled endogenous lipids by isolated perfused rat heart, Science 143:371, 1964.
190. Olson, R. E.: Effects of pyruvate and acetoacetate on the metabolism of fatty acids by the perfused rat heart, Nature 195:597, 1962.
191. Mansford, K. R. L., and Opie, L. H.: Effect of heart work on glucose uptake and glycolysis in hearts from normal and diabetic rats, Biochem. J. 105:28P, 1967 (Abst.).
192. Marquis, N. R., and Fritz, I. B.: Enzymological determination of free carnitine concentrations in rat tissues, J. Lipid Res. 5:184, 1964.
193. Fritz, I. B., and Yue, K. T. N.: Long-chain carnitine acyltransferase and the role of acylcarnitine derivatives in the catalytic increase of fatty acid oxidation induced by carnitine, J. Lipid Res. 4:279, 1963.
194. Friedberg, S. J., and Bressler, R.: The formation and isolation of long-chain acyl carnitines in mitochondria, Biochim. Biophys. Acta 98:335, 1965.
195. Korsberg, A., and Prieur, W. E., Jr.: Enzymatic synthesis of the coenzyme A derivatives of long-chain fatty acids, J. Biol. Chem. 204:329, 1953.
196. Fritz, I. B.: Carnitine and its role in fatty acid metabolism, Advances Lipid Res. 1:286, 1963.
197. Bremer, J.: Carnitine in intermediary metabolism. The biosynthesis of palmitylcarnitine by cell subfractions, J. Biol. Chem. 238:2774, 1963.
198. Fritz, I. B., and Marquis, N. R.: The role of acylcarnitine esters and carnitine palmityltransferase in the transport of fatty acyl groups across mitochondrial membranes, Proc. Nat. Acad. Sc. 54:1226, 1965.
199. Shepherd, D., Yates, D. W., and Garland, P. B.: The rate-limiting step in the oxidation of palmitate or palmitylCoA by rat liver mitochondria, Biochem. J. 98:3c, 1966.
200. Bode, C., and Klingenberg, M.: Carnitine and fatty acid oxidation in mitochondria of various organs, Biochim. Biophys. Acta 84:93, 1964.
201. Vahouny, G. V., Katzen, R., and Entenman, C.: Myocardial metabolism. II. Role of nutritional state and glucose oxidation by isolated perfused hearts, Biochim. Biophys. Acta 137:181, 1967.
202. Bremer, J.: Carnitine in intermediary metabolism. Reversible acetylation of carnitine by mitochondria, J. Biol. Chem. 237:2228, 1962.
203. Bremer, J.: Carnitine in intermediary metabolism. The metabolism of fatty acid esters of carnitine by mitochondria, J. Biol. Chem. 237:3628, 1962.
204. Wittels, B., and Bressler, R.: Biochemical lesion of diphtheria toxin in the heart, J. Clin. Invest. 43:630, 1964.
205. Bressler, R., and Wittels, B.: The effect of diphtheria toxin on carnitine metabolism in the heart, Biochim. Biophys. Acta 104:39, 1965.
206. Orth, D. N., and Morgan, H. E.: The effect of insulin, alloxan diabetes, and anoxia on the ultrastructure of the rat heart, J. Cell. Biol. 15:509, 1962.
207. Denton, R. M., and Randle, P. J.: Measurement of flow of carbon atoms from glucose and glycogen glucose to glyceride glycerol and glycerol in rat heart and epididymal adipose tissue. Effects of insulin, adrenaline and alloxan-diabetes, Biochem. J. 104:423, 1967.
208. Garland, P. B., and Randle, P. J.: Regulation of glucose uptake by muscle. 10. Effects of alloxan-diabetes, starvation, hypophysectomy and adrenalectomy, and of fatty acids, ketone bodies and pyruvate on the glycerol output and concentrations of free fatty acids, long-chain fatty acyl CoA, glycerol phosphate and citrate-cycle intermediates in rat heart and diaphragm muscles, Biochem. J. 93:678, 1964.
209. Warnen, C.: Studies in lipid mobilization, Acta physiol. scandinav. 65(Suppl. 252), 1965.
210. Ferrans, V. J., Hibbs, R. G., Black, W. C.

and Weilbaecher D G. Isoproterenol-induced myocardial necrosis. A histochemical and electron microscopic study Am. Heart J 68 71 1964
211 Ferrans, V J Hibbs, R. G. Weilbaecher D G., Black W C. Walsh J J and Burch, G. E. Alcoholic cardiomyopathy Am. Heart J 69 748, 1965
212 Harris, P Fletcher R. F Gloster J and Gotsman, M The metabolism of glycerol and free fatty acids during exercise in patients with rheumatic heart disease, Clin. Sc. 28:343, 1965
213. Kreisberg R A Effect of diabetes and starvation on m ocardial triglyceride and free f tty acid tilization Am J Physiol. 210:379 1966
213A Robinson, J and Newsholme, E. A. Glycerol kinase activ ties in rat heart and adipose tissue, Biochem J 101:2c, 1967
214 Scheuer J and Olson, R. E. Metabolism of exogenous triglyceride by the isolated perfused rat heart, Am J Physiol. 212:301 1967
215 Delcher H K Fried, M and Shipp, J C.: Metabolism of lipoprotein lipid in the isolated perfused rat heart, Biochim. et biophys. acta 106 10 1965
216. Hall, L. M Preferential oxidation of acetoacetate by the perfused heart, Biochem. Biophys Res Comm 6 177 1961
217 Bing, R. J Siegel, A Ungar I and Gilbert, M Metabolism of the human heart. II Studies on fat, ketone and ammonoid metabolism Am J Med 16:504 1954
218 Bassenge E Wendt, V E. Schollmeyer P Bl mchen G. Gudbjarnason, S and Bing, R J Effect of ketone bodies on cardiac metabolism, Am. J Physiol. 208 162, 1965
219 Rudolph, W Maas, D Richter J Ha singer F Hofmann, H and Dohrn, P Über die Bedeutung von Acetoacetate und β-hydroxybutyrat im Stoffwechsel des menschlichen Herzens, Khn. Wchnsch 43:445 1965
220. Green, D E Dewan J G., and Leloir L. F The β-hydroxybutyric dehydrogenase of nimal tissues, Biochem. J 31:934 1937
21 Stern, J R Coon, M J and del Campillo, A. Enzymes of f tty acid metabolism. III Breakdow and sy thesis of β-keto f tty cids, J Biol. Chem 221 1 1956
222. Lehninger A L. Sudd th H C. and Wise J B. D-β-hydroxybutyric dehydrogenase of mitochondria, J Biol Chem 235:1450, 1960.
223 Krebs H A and Eggleston, L V Metabolism f acetoacetate I animal tissues. 2, Biochem. J 42:294 1948
224 Kulka, R. C Krebs, H A nd Eggleston, L. V The reduct n f acetoacetat to β-hydroxybutyr t m imal tissues Biochem. J 78:95 1961
225 Williamson, D H Lund I nd Krebs, H A. The redox t t f icotinamide-adenine dinucleotide in the cytopla m and mitochondria of rat liver Biochem J [illegible] 514 1967
226. Borst, P Hydrogen transport and transport metabolites, in Funktionelle und Morphologische Organisation der Zelle [illegible] ferenz der Gellschaft Deutscher [illegible] und Ärzte, 1962, Berlin, 1963, [illegible] Verlag, p. 137
227 Williamson, D H., Mellanby J and Krebs H. A. Enzymic determination of D(-) hydroxybutyric acid and acetoacetic acid in blood, Biochem. J 82:90, 1962.
228. Krebs, H. A. The biochemical [illegible] ketosis, Arch. I t. Med. 107:51, 1961.
229 Stein, Y and Stein, O.: Uptake of [illegible] P32-lysolecithin by the isolated perfused rat heart, Life Sci. 3:883, 1964.
230. Robinson, D S. The physiological significance of the plasma triglycerides in [illegible] transport, in Dawson, R. M. C. and [illegible] D N editors Metabolism and physiological significance of lipids, London, 1964, [illegible] & Sons p. 275
231 Havel, R. J Felts, J M., and Van Duyne C. M Formation and fate of endogenous triglycerides in blood plasma of rabbits J Lipid Res. 3:297 1962.
232. Reaven, G. M Hill, D B Gross, R. C. and Farquhar J W Kinetics of triglyceride turnover of very low density lipoproteins of human plasma, J Clin. Invest. 44:[illegible] 1965.
233. Bezman-Tarcher A., Otway S and Robinson, D S. Th removal of triglyceride fatty acids from the circulation of the [illegible] diaphragmatic portion of the rat, Proc R Soc., series B 162:411 1965
234 Crass, M F III, and Meng, H. C. The removal and metabolism of ch lomicron triglycerides by the isolated perfused heart the role of heparin-released lipase Biochim. Biophys. Acta 125:106, 196[illegible]
234A. Goto, Y Hasega a, T Takasaka, [illegible] Kanda, A., Mori, K., Katayama, T [illegible] shida, K., Nagano, S Wakamura, H [illegible] S. nd Kato, M. Experimental study on the lipid metabolism in the heart muscle, Jap Circ. J 28:301 1964
235 Goto, Y The fatty metabolism in the muscle, Jap. Circ. J 26 121 1962.
236 Gousios, A., Felts, J M and Havel, R J The metabolism of serum triglycerides and free f tty acids by the myocardium Metabolism 12 75 1963.
237 Bragdon, J H nd Gordon, R. S. Jr Tissue distribution of labelled cholesterol and unesterified fatty acids in the rat, J Clin I vest. 37:574 1958.
238. Ontko, J A., and Randle P J [illegible] of glucose tilization by perfused [illegible] chylomicrons in rat heart, Biochem J 104:43c 1967
239 Morris, B nd Simpson-Morgan, M W Effect of glucose on the metabolism of [illegible] fused hylomicron f tty acids in the [illegible] anaesthetized rats, J Physiol 1[illegible]
240 Borgström, B nd Jorda J Metabol[illegible]

of chylomicron glyceride as studied by C14-glycerol-C14 palmitic acid labelled chylomicrons, Acta Soc. Med. Upsal. 64: 185, 1959.
1. Olivecrona, T.: Metabolism of chylomicrons labelled with C14-glycerol H3-palmitic acid in the rat, J. Lipid Res. 3: 439, 1962.
41A. French, J. E.: The behaviour of chylomicrons in the circulation. Observations with the electron microscope, in Frazer, A. C., editor: Biochemical problems of lipids, Amsterdam, 1963, Elsevier Publishing Company. Biochim. Biophys. Acta Library, vol. 1, p. 296.
42. Robinson, D. S., and French, J. E.: Heparin, the clearing factor lipase and fat transport, Pharmacol. Rev. 12: 241, 1960.
43. Robinson, D. S.: The clearing factor lipase and its action in the transport of fatty acids between the blood and the tissues, Advances Lipid Res. 1: 133, 1963.
44. Korn, E. D.: Clearing factor, a heparin-activated lipoprotein lipase. I. Isolation and characterization of the enzyme from normal rat heart, J. Biol. Chem. 215: 1, 1955.
45. Schatz, J. D., Ormsby, J. W., and William, R. H.: Lipoprotein lipase activity in human heart, Am. J. Physiol. 205: 401, 1963.
46. Alousi, A. A., and Mallov, S.: Effects of hyperthyroidism, epinephrine, and diet on heart lipoprotein lipase activity, Am. J. Physiol. 206: 603, 1965.
47. Mallov, S., and Alousi, A. A.: Effect of altered cardiac metabolism and work on lipoprotein lipase activity in heart, Am. J. Physiol. 212: 1158, 1967.
48. Kessler, J. I.: Effect of diabetes and insulin on the activity of myocardial and adipose tissue lipoprotein lipase of rats, J. Clin. Invest. 42: 362, 1963.
49. Hollenberger, C. H.: The effect of fasting on the lipoprotein lipase activity of rat heart and diaphragm, J. Clin. Invest. 39: 1282, 1960.
250. Robinson, D. S., and Jennings, M. A.: Release of clearing factor lipase by the perfused rat heart, J. Lipid. Res. 6: 222, 1965.
251. George, J. C., and Iype, P. T.: A study of the lipase activity in the developing chick heart, J. Exper. Zool. 141: 291, 1959.
252. Nikkilä, E. A., Torsti, P., and Penttilä, O.: The effect of exercise on lipoprotein lipase activity of rat heart, adipose tissue and skeletal muscle, Metabolism 12: 863, 1963.
253. Kreisberg, R. A.: Effect of epinephrine on myocardial triglyceride and free fatty acid utilization, Am. J. Physiol. 210: 385, 1966.
254. Mallov, S., and Cerra, F.: Effect of ethanol intoxication and catecholamines on cardiac lipoprotein lipase activity in rats, J. Pharmacol. & Exper. Therap. 156: 426, 1967.
255. Fisher, R. B., and Williamson, J. R.: The effects of insulin, adrenaline and nutrients on the oxygen uptake of the perfused rat heart, J. Physiol. 158: 102, 1961.
256. Willebrands, A. F., and van der Veen, K. J.: Influence of substrate on oxygen consumption of isolated perfused rat heart, Am. J. Physiol. 21: 1529, 1967.
257. Challoner, D. R., and Steinberg, D.: Oxidative metabolism of myocardium as influenced by fatty acids and epinephrine, Am. J. Physiol. 211: 897, 1966.
258. Neely, J. R., Liebermeister, H., and Morgan, H. E.: Effect of pressure development on oxygen consumption by isolated rat heart, Am. J. Physiol. 12: 804, 1967.
259. van der Veen, K. J., and Willebrands, A. F.: Effect of frequency and Ca^{++} concentration on oxygen consumption of the isolated rat heart, Am. J. Physiol. 12: 1536, 1967.
260. Randle, P. J., Hales, C. N., Garland, P. B., and Newsholme, E. A.: The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus, Lancet 1: 785, 1963.
261. *Williamson, J. R.: Metabolic effects of epinephrine in the isolated perfused rat heart,* J. Biol. Chem. 239: 2721, 1964.
262. Vahouny, G. V., Katzen, R., and Entenman, C.: Glucose uptake by isolated perfused hearts from fed and fasted rats, Proc. Soc. Exper. Biol. & Med. 121: 923, 1966.
263. Opie, L. H.: Fatty acids and the heart. (Letter) Lancet 2: 366, 1963.
264. Shipp, J. C.: Interrelation between carbohydrate and fatty acid metabolism of isolated perfused rat heart, Metabolism 13: 852, 1964.
265. Hirche, H., and Koike, S.: Hemmung der Aufnahme und des Abbaues der Glucose im Herzmuskel narkotisierter Hunde durch die freien Fettsauren, Pflüger. Arch. Physiol. 280: 158, 1964.
266. Hirche, H. J., and Langohr, H. D.: Hemmung des Milchsäureentnahme im Herzmuskel narkotisierter Hunde durch hohe arterielle Konzentration der freien Fettsäuren, Pflügers Arch. Physiol. 293: 208, 1967.
267. Davis, E. J., and Quastel, J. H.: The effects of short-chain fatty acids and starvation on the metabolism of glucose and lactate by the perfused guinea pig heart, Canad. J. Biochem. 42: 1605, 1964.
268. Olson, R. E.: Abnormalities on myocardial metabolism, in Evans, J. R., editor: Structure and function of heart muscle. Circulation Res. (Suppl. 11) 15: 343, 1964.
269. Blanchaer, M. C.: Respiration of mitochondria of red and white skeletal muscle, Am. J. Physiol. 206: 1015, 1964.
270. Pette, D., Luh, W., and Bücher, Th.: A constant-proportion group in the enzyme activity pattern of the Embden-Meyerhof chain, Biochem. Biophys. Res. Commun. 7: 419, 1962.
271. Dubowitz, V., and Pearse, A. G. E.: Reciprocal relationship of phosphorylase and oxidative enzymes in skeletal muscle, Nature 185: 701, 1960.
272. George, J. C., and Jyoti, D.: Histological features of the breast and leg muscles of bird and bat and their physiological evolutionary significance, J. Anim. Morphol. Physiol. 2: 31, 1955.

273 George J C., and Scaria, K. S.: Histochemical demonstration of lipase activity in the pectoralis major muscle of the pigeon, Nature 181 783 1958.

274. George J C., and Naik, R. M: Relative distribution and chemical nature of the fuel store of the two types of fibres in the pectoralis major muscle of the pigeons, Nature 181 709 1958.

275 Bilinski, E Utilization of lipids by fish. I F tty acid oxidation by tissue slices f om dark nd white muscle rainbow trout (Salmo Gairdnerii) Canad J Biochem. 41:107 1963

276. Dehaan, R L Differentiation of the atrioventricular conducting system of the heart, Circulation 24:458, 1961

277 W ttels, B and Bressler R Lipid metabolism in the new born heart, J Clin. I vest. 44 1639 1965

278 Opie, L H Coronary flow rat and perfusion pressure as determinants of mechanical function and oxidative metabolism of isolated perfused rat heart J Physiol 180:529 1965

279 Arnold G Kosche F Miessner E Neitzert, A nd Lochner W The importance of the perfusion pressure in the coronary arteries for the contractility and the oxygen consumption of the heart, Pflugers Arch Physiol 299:339 1968

280 Morg n, H E. Personal communication.

281 Shipp, J C., and Crass, M F III. Personal communication

282 Harris, P Jones, J H Bateman, M Chlouverakis, C and Gloster J M tabolism of the myocardium t rest and during exercise in patients with rheumatic heart disease, Clin. Sc. 26 145 1964

283 Gregg, D E The coronary circulation i the unanaesthetized dog Coronary circulation nd energetics of the myocard um Basel/New York, 1967 S Karger p 54

284 Shipp, J C M tos, O E. Kolsley H and Crevasse, L. E CO_2 formed f om endogenous and exogenous substrates in perfused rat heart Am J Physiol 207 1231 1964

285 Williamson, J R Effects of insulin and starvation on the metabolism of acetat and pyruvat by the perfused rat heart, Biochem. J 93:97 1964

286. Olson, R E. and Piatnek D A. Conservation of energy in cardiac muscle A New York Acad. Sc. 72:466, 1959

287 Gordon, R S., J Unesterified fatty acid in human blood plasma. II The tran port function of unesterified f tty acid, J Clin I vest. 36:810 1957

287A. Michal, G Naegle, S Danforth, W H Ballard, F B., nd Bing, R. J Metabolic changes in heart muscle during noxia, Am. J Physiol 197 1147 1959

288. Bücher Th. and Klingenberg M Wege der W sserstoff in der lebendigen org isation, Angew and Chem. 70:552 1958.

289 Lee, Y and Lardy H. A. Influence of thyroid hormones on L-α-glycerophosphate dehydrogenase and other dehydrogenases in various organs of the rat, J Biol Chem 240 1427 1965.

290. Pette D: Plan und Muster in zellulären Stoffwechsel, Naturwissenschaften 52 1965

291 Kraus, A.: Das Kompensationsphänomen der Glycerin-1-phosphate-oxydase ... und Bücher in Skelet und Herzmuskel verschiedener Tierklassen. (Ratte und ...be) Pflügers Arch. Physiol. ...

292. Deshpande, P D Hickman, D D ... Von Korff R. W: Morphology of isolated rabbit heart mitochondria and the oxidation of extramitochondrial reduced diphosphopyridine nucleotide, J Biophys Biochem Cytol. 11 77 1961.

293 Griffith, T J and Blanchaer M. C. Kinetics of NADH oxidation by ... mitochondria, Canad. J Biochem. ... 1967

294 Ulrich, F: Active transport of potassium by heart mitochondria, Am. J Phys... 198:847 1960.

295 Brierley G. P: Ion accumulation in heart mitochondria, *in* Chance B Estabrook R. W and Williamson, J R., editors: Energy-linked functions of mitochondria New York, 1963, Academic Press, Inc. p. 237

296. Brierley G., Murer E., Bachmann, E., and Green, D E. Studies on ion transport ... The accumulation of inorganic phosphate and magnesium ions by heart mitochondria, J Biol. Chem. 238:3482, 1963

297 Lehninger A. L., Carafoli, E., and Rossi, C. S.: Energy linked ion movements in mitochondrial systems, Advances Enzym. 29:260, 1967

298. Lardy H A., Connelly J L., and Johnson, D: Antibiotics as tools for metabolic studies. II Inhibition of phosphoryl transfer in mitochondria by oligomycin and aurovertin, Biochemistry 3:1961 1964.

299 Rasmussen H., and Ogata, E.: Cation ... across the mitochondrial membrane as a possible pacemaker of tissue metabolism, *in* Chance B Estabrook, R. W and Williamson, J R. editors. Control of energy metabolism, New York, 1965 Academic Press, Inc. p. 209

300. Bowman, R. H Effects of diabetes, fatty acids and ketone bodies on tricarboxylic acid cycle metabolism in the perfused rat heart, J Biol. Chem. 241:3041, 1966

301 Wieland, O and Weiss, L.: Inhibition of citrate-synthase by palmityl-coenzyme A, Biochem. Biophys. Res. Commun. ... 1963.

302. Kosicki, G W nd Lee L. P K.: Effect of divalent metal ions on nucleotide inhibition of pig heart citrat ynthase J Biol Chem 241:3571 1966.

303 Fritz, I B. Relief of palmityl CoA ...

tion of citrate synthase by long-chain acylcarnitine derivatives, Biochem. Biophys. Res. Commun. 22 744 1966.
304. Wieland, O., Weiss, L., and Eger Neufeldt, I. Hemmung der enzymatischen Citronensäuresynthese durch langkettige Acyl-Thioester des Coenzyme A, Biochem. Ztschr 339:501 1964
305. Srere, P A. The citrate cleavage enzyme. I Distribution and purification, J Biol. Chem. 234:2544 1959
305A. England, P J Denton, R. M and Randle P J The influence of magnesium ions and other bivalent metal ions on the aconitase equilibrium and its bearing on the binding of magnesium ions by citrate in rat heart, Biochem. J 105:31c, 1967
306. Sanwal, B. D Zink, M W and Stachow C. S. Control of DPN-specific isocitric dehydrogenase activity by precursor activation and end product inhibition, Biochem. Biophys. Res. Commun. 12:510 1963.
307 Chen, R. F and Plaut, G W E. Activation and inhibition of DPN-linked isocitrate dehydrogenase of heart by certain nucleotides, Biochemistry 2 1023, 1963
308. Goebell, H., and Klingenberg, M DPN specifische Isocitrat Dehydrogenase des Mitochondrien. I Kinetische Eigenschaften, Vorkommen und Funktion der DPN-spezifischen Isocitrat Dehydrogenase, Biochem Ztschr 340:441 1964.
309 Klingenberg, M Goebell, H and Wenske. G. DPN-specific isocitrate dehydrogenase of mitochondria. II. pH-dependence and kinetics of mechanism of action, Biochem Ztschr 431 199 1965.
310. Plaut, G. W E., and Plaut, K. A Oxidative metabolism of heart mitochondria, J Biol. Chem. 199:241 1952.
311 Bowman, R. H Fatty acid induced alterations in citric acid cycle intermediates, Chance, B Estabrook, R W and Williamson, J R., editors Control of energy metabolism, New York, 1965, Academic Press, Inc., p 357
312. Schollmeyer P and Klingenberg, M Oxaloacetate and adenosinetriphosphate levels during inhibition and activation of succinate oxidation, Biochem. Biophys Res. Commun. 4:43 1961
313. Davies, D D and Kun, E. Isolation and properties of malic dehydrogenase from ox heart mitochondria, Biochem. J 66:307 1957
314. Heldt, H. W Jacobs, H., and Klingenberg, M Endogenous ADP of mitochondria, an early phosphate acceptor of oxidative phosphorylation as disclosed by kinetic studies with C^{14} labelled ADP and ATP and with atractyloside Biochem. Biophys. Res. Commun. 18 174 1965
315. Klingenberg, M and Pfaff E Structural and functional compartmentation in mitochondria, in Tager J M Papa, S., Quagliariello, E., and Slater E. C., editors Regulation of metabolic processes in mitochondria, Amsterdam 1966, Elsevier Publishing Company p. 86
316. Challoner D R., and Steinberg D Metabolic effect of epinephrine on the oxygen consumption of the perfused rat heart, Nature 205:602 1965.
316A. Challoner D R. Respiration in myocardium, Nature 217 78, 1968.
317 Furchgott, R F and Lee K. S. High energy phosphates and the force of contraction of cardiac muscle, Circulation 24:416, 1961.
318 Feinstein, M B Effects of experimental congestive heart failure, ouabain and asphyxia on the high energy phosphate content and creatine content of the guinea pig heart, Circulation Res 10:333 1962.
319 Fleckenstein, A. Die Bedeutung der energiereichen Phosphorphate fu Kontraktilitat und Tonus des Myokards, Verh. Deutsch. Ges. Inn. Med. 70:81 1964
320 Fox, A C and Reed, G. F Exchanges of nucleotide phosphates in normal and failing canine hearts, Am. J Physiol. 210 1383, 1966
321 Pool P E Spann, J F J Buccino, R. A., Sonnenblick, E. H. and Braunwald, E. Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure Circulation Res. 21:365, 1967
322 Watanabe S and Packer L. Oxidative phosphorylation of cardiac mitochondria in contraction of glycerol-treated fibers of psoas muscle, J Biol. Chem. 236 1201 1961.
323 Harary I and Slater E. C Studies in vitro on single beating heart cells VIII The effect of oligomycin, dinitrophenol, and ouabain on the beating heart, Biochim Biophys. Acta 99:227 1965
324. Challoner D R Hypermetabolic states, Lancet 2:681 1966.
325 Cain, D F and Davies, R. E Breakdown of triphosphate during single contraction of working muscle, Biochem. Biophys. Res Commun. 8:361 1962.
326. Infante, A. A and Davies, R. E Adenosine triphosphate breakdown during a single isotonic twitch of frog sartorius muscle Biochem. Biophys. Res. Commun. 9:410, 1962.
327 Mommaerts, W F H M and Wallner A. The break-down of adenosine triphosphate in the contraction cycle of the frog sartorius muscle, J Physiol. 193:343 1967
328. Whittam, R. The interdependence of metabolism and active transport, in Hoffman, J F editor Cellular functions of membrane transport, Englewood Cliffs, N J 1964 Prentice Hall, Inc., p. 139
329 Chance, B and Williams, G. R. The respiratory chain and oxidative phosphorylation, Advances Enzym. 17:65 1956.
330 Lardy H. A., and Wellman, H. Oxidative phosphorylations role of inorganic phosphate and acceptor systems in control of

metabolic rates, J Biol. Chem. 195:215 1952.

331 Plechaty M Gertler M M and Guthrie, R G. Intramitochondrial uptake of ³²P in adenine ucleotides in congestive heart failure, Biochim. Biophys. Acta 127:524, 1967

332. Janke, J Marmier P and Fleckenstein, A. Die Bestimmung der absol ten Umset zungsraten von ATP Kreatinphosphat und Orthophosphat in der ruhenden Skelet musk latur mit Hilfe Von H_2O^{18} la Tracer Pflügers Arch Physiol. 282:119 1965

333 Ochoa, S. Efficiency of aerobic phosphoryla tion in cell-free heart extracts, J Biol. Chem. 151:493 1943

334. Haugaard N Ineu, G and Haugaard, E. S Glucose oxidation and high energy phosphate production in heart homogenates, Circulation Res 11:381 1962.

335 Szekeres, L and Schein, M Cell metabolism of the overloaded mammalian heart in situ Cardiologica 34 18 1959

336. Schwartz, A. and Lee, K. S. Study of heart mitochondria and glycolytic metabolism in experimentally induced cardiac failure Cir culation Res 10:321 1962.

337 Argus, M F Arcos, J C. Sardesai, V M and Overb J L Oxidative rates nd phosphorylation in sarcosomes from experimentally induced failing rat heart, Proc. Soc. Exper Biol. & Med 117:380, 1964

338. Fox, A. C Wikler N S. and Reed, G. E. High energy phosphate compounds in the myocardium during experimental congestive heart f ilure. Purine and pyrimidine nucleotides creatine and creatine phosphat in normal and failing hearts, J Clin I vest. 44:202 1965.

339 Gertler M M Murakami, K., and Guthrie, R. G. Oxidative phosphorylation in ormal and failure liver kidney and heart mitochondria, Proc. Soc. Exper Biol. & Med 121:657 1966

340. Procita, L., Schwartz A and Lee, K. S. Oxidati e phosphorylation in the failing dog heart-l ng preparation, Circulation Res. 16:391 1965

341. Wollenberger A and Sch lze, W Mitochondrial alterations in the myocardium of dogs with aortic stenosis, J Biophys. Biochem. Cytol. 10:285, 1961

342 Wollenberger A Kleitke, B nd Raabe, G. Some metabolic haracteristics of mitochondria f om chemically overloaded hypertrophied hearts, Exp. Molec. Path. 2:251 1963

343. Wollenberger A. The energy metabolism of the failing heart and the metabolic action of cardiac glycosides, Pharm Rev 1:311 1949

344 Furchott R F nd de Gubareff T The high energy phosphat content of cardiac m scle nder v rious experiment l condition which alter contractile strength J Pharmacol. & Exper Therap. 121:203 1958.

345 Buckley N M and Tsabol, K K Cr nucleotides and derivatives in acu e chronic ventricular failure of the dog Circulation Res. 9:618, 1961.

346. Chidsey C. A., Weinbach, E. C, Pa P E., and Morrow A. G. Biochem studies of energy production in the f human heart, J Clin. Invest. [illegible]

347 Sobel, B. E., Spann, J F Jr Pool, P E Sonnenblick, E. H., and Braunwald E Normal oxidative phosphorylation in mitochondria from the failing heart, Circ. Res. 21:355, 1967

348. Opie, L. H Lochner A., Brink, A. J., Fr burger F and Nixon, C. W. Oxid phosphorylation in hereditary myocardi athy in the Syrian hamster [illegible] 1964

349 Sundermeyer J F Gudbjarnason, S Wendt, V E. den Bakker P B and Bi R. J Myocardial metabolism in progressive muscular dystrophy Circulation [illegible] 1961

350. Eppenberger M Nixon, C. W Ba J R., and Homburger F Serum phosphocreatine kinase in hereditary muscular dystrophy and cardiac necrosis of Syr golden hamsters, Proc. Soc. Exper. Biol. & Med. 117:465, 1964

351 Homburger F Baker J R Nixon, C. W. Wilgram G., and Harrop, J The ori histopathological lesion of muscular dystrophy in the Syria golden hamster, J Path. & Bact. 89 133 1965.

352. Homburger F Baker J R., and Nixon C. W Myopathic Syrian hamsters as disease models of muscular dystrophy and congestive heart failure Fed. Proc. [illegible] 1966 (abstr)

353. Christ, E. J and Hülsmann, W. C. S thesis of long-chain fatty acids by mito chondrial enzymes, Biochim. Biophys Acta 60 72, 1962.

354 Hulsmann, W C. On the synthesis of malonyl-coenzyme A in rabbit-heart sarcosomes, Biochim. Biophys Acta [illegible] 1966

355 Wherent, A F Hull, F E Orishimo W and Rabinowitz, J L. The role of cinate in the regulation of fatty acid synthesis by heart mitochondria, J Biol Chem 212:4013 1967

356. H ll, F E., nd Whereat, A. F The effect of rot none on the regulation of fatty acid synthesis i heart mitochondria, J Biol Chem. 212:4023 1967

357 Hülsman W C., Wit-Peeters E. M and Benckh ysen, C. Factors influencing fatty acid metabolism in mitochondria, in Tager J M Papa, S Quagliariello, E., nd Slater E. C., editors: Regulation of metabolic processes in m tochondria, Amsterdam, 1966, Elsevier Publishing Company p [illegible]

358 Christ F J [illegible] fatty acid [illegible] mitochondria. [illegible] of short-chain fatty acid and formation of saturated long chain f tty acids, Biochim. et Biophys Acta 152:50, 1968

359. Lynen, F Henning, U Bublitz, A., Sorbo, B., and Kröplin-Rueff L. Der Chemische Mechanismus der Acetessigsäurebildung in der Leber Biochem. Ztschr 330:269 1958
360. Bachhawat, B. K., Robinson, W G and Coon, M. J The enzymatic cleavage of β-hydroxy-β-methylglutaryl coenzyme A to acetoacetate and acetyl coenzyme A J Biol. Chem. 216 727 1955
361. Stern, J R., Coon, M J and del Campillo, A. Enzymes of fatty acid metabolism. III Breakdown and synthesis of β-keto fatty acids, J Biol. Chem. 221 1 1956.
362. Matsubara, H. Studies on myocardial protein metabolism J p. Circ J 26:27 1962
363. Schreiber S. S. Oratz, M and Rothschild, M A Protein synthesis in the overloaded mammalian heart, Am J Physiol 211:314 1966.
364. Scharff R., and Wool, I. G. Accumulation of amino acids in muscle of perfused rat heart Effect of insulin, Biochem J 97:257 1965.
365. Doell, R. G and Feltz, J M Metabolism of glutamic acid in the perfused rabbit heart Am. J Physiol. 197 138, 1959
366. Hicks, R. M and Kerly M Transaminase activity in the perfused rat heart, J Physiol 150:621 1960.
367. Earl, D C. N and Korner A. The isolation and properties of cardiac ribosomes and polysomes, Biochem. J 94 721 1965
368. Earl, D C. N and Korner A Effect of rat hypophysectomy and growth hormone treatment on cardiac polysomes ribonucleic acid, Arch. Biochem Biophys 115:445 1966.
369. Rampersad, O R. Zak, R Rabinowitz, M Wool, I. G., and DeSalle, L. Isolation and characterization of ribonucleoprotein particles from heart muscle, Biochim. Biophys. Acta 108:95, 1965
370. Posner B. I and Fanburg, B L. Studies on components of RNA in cardiac muscle with emphasis on the rapidly labelled 4 to 18 S fraction, Circulation Res. 19:805 1967
371. Roodyn, D B. Factors affecting the incorporation of amino acids into protein by isolated mitochondria, in Tager J M Papa, S., Quagliariello, E., and Slater F C editors Regulation of metabolic processes in mitochondria, Amsterdam, 1966, Elsevier Publishing Company p 383
372. Manchester K. L. and Wool, I G. Insulin and incorporation of amino acids into protein of muscle. 2. Accumulation and incorporation studies with the perfused rat heart, Biochem. J 89:202, 1963
373. Scharff R., and Wool, I. G Accumulation of amino acids in muscle of the perfused rat heart. Effect of insulin in the presence of puromycin, Biochem. J 97:272, 1965
374. Wool, I R., Rampersad, O R., and Moyer A. N Effect of insulin and diabetes on protein synthesis by ribosomes from heart muscle, Am J Med 40 716, 1966.
375. Wagle S R. The influence of growth hormone cortisol and insulin on the incorporation of amino-acid into protein, Arch Biochem. 102:373 1963
376. Beznak, M. The influence of anterior pituitary hormones in controlling size, work and strength of the heart, J Physiol. 150:251 1960.
377. De Grandpré R. and Raab, W Interrelated hormonal factors in cardiac hypertrophy Experiments in nonhypertensive hypophysectomized rats, Circulation Res. 1:345 1953.
378. Meerson, F Z. Kalebina, N S., and Malov G. A. Effect of actinomycin D on the development of the compensatory hyperfunction of the myocardium kidney and liver Acta Biol Acad. Sci Hung 15:375 1965
379. Gudbjarnason, S Telerman, M and Bing R. J Protein metabolism in cardiac hypertrophy and failure Am. J Physiol. 206:394 1964.
380. Hanking, B M and Roberts, S. Stimulation of protein synthesis in vitro by elevated levels of amino acids, Biochim. Biophys. Acta 104:427 1965
381. Moroz, L R. Protein synthetic activities of heart microsomes and ribosomes during left ventricular hypertrophy in rabbits, Circulation Res. 21:449 1967
382. Muller E and Pearse, A. G E Localization of monoamine oxidase in mammalian and reptilian heart, Brit. Heart J 27 116 1965
383. Carbonell, L. M Esterases of the conductive system of the heart, J Histochem Cytochem. 4:87 1956.
384. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart, J Physiol. 4:29 1883
385. Schildberg, F W and Fleckenstein, A Die bedeutung der extracellularen Calcium konzentration fur die Spaltung von energiereichen Phosphat in ruhenden und tätigem Myokardgewebe Pflugers Arch Physiol. 283:137 1965
386. Seifen, E Flacke W and Alper M H Effects of calcium on isolated mammalian heart, Am. J Physiol. 207 716 1964.
387. Niedergerke, R Movements of Ca in beating ventricles of the frog heart, J Physiol 167:551 1963
388. Hajdu, S., and Leonard, E Binding of cardioglobulin-C-Ca++ to cardiac muscle and release by cardioglobulin A, Am. J Physiol. 209 1 1965.
389. Weber A., and Herz, R. The binding of calcium to actomyosin systems in relation to their biological activity J Biol Chem. 238:599 1963
390. Seidel, J C., and Gergely J Contraction of glycerinated muscle fiber and the role of calcium, Biochem. Biophys. Res. Commun. 13:343, 1963
391. Seidel, J C and Gergely J Studies on myofibrillar adenosine triphosphatase with calcium-free adenosine triphosphate I The

eff t of thylenediaminetet aacetate calcium magnesium and adenosine triphosphate J Biol Chem 238:3648 1963
392 Weber A Herz, R and Reiss, I The reg lation of myofibrillar act vity by calcium, Proc. Roy Soc. series B 160:489 1964
393 Levy H M and Ryan, E M Evidence that calcium activ tes the contraction of actomyosi by overcom ng substrate inhibition, N ture 205 703, 1965
394 Winegrad, S and Shanes, A M Calcium flux nd ontract lity i gu nea pig atria, J Gen Physiol 45:371 1962
395 Langer G A and B ady A J Calcium flux the mammalian entricular m ocard um J Ge Physiol 46 703 1963
396. Bozler E Mechan sm of relaxation of extracted muscle fibers Am J Ph siol 167:276, 1951
397 Hasselbach W ATP-driven active transport of calc m the membranes of the sarcoplasmic reticul m P oc Roy Soc. series B 160 501 1964
398 Carsten M J The ardiac alcium pump I oc N t Acad Sc 5. 1456 1964
399 Leona d F nd H jd S Cardioglobul n. Clinical orr lations, Cir ulation Res 9:891 1961
400 Nieu nd jk F S De vloed van calcium op de mecha sche activiteit an het geisoleerde rt hart, Academic Thesis, Univer t of Am terdam 1966
401 L t g H C nd Niedergerk R The tag nism between Ca and N ion on the f g he rt J Phy iol 143:486 1958
402 Gilbert, D L nd Fenn W O Calcium eq ilibrium muscle J Gen. Physiol 40 393 195
403 N ler W G C lcium exchange i cardiac muscle ba mechanism of drug action, Am Heart J 3 379 1967
404 Portzehl H Cald B P C and Rüegg J C The dependence of contraction and relaxation of m scle fibres f om the crab Maia Sq ad on the internal concentration of the alc um ion Biochim Bioph s Acta 9:581 1964
405 Weber A Herz, R and Reiss I On the mechan sm of the lax ng effect of fragmented sar opla mic reticul m, J Gen. Physiol 46:679 1963
406 Niedergerke R The te of action of calcium ion on the ont action of the heart J Ph iol 138:506 1957
40 Winegrad, S A t radiogr phic studies of intracell lar alcium in frog sk letal muscle, J Gen. Physiol 48 455 1965
408. N lson D A nd Benson E S On the tructural contin ities of the tran verse tubular ystem of abbit and hum n m ocardial cells J Cell Biol. 16:297 1963
409 Lee K S. Effect of electrical stimulation on uptake and release of calcium by endoplasmic reticul m Nature 207:85, 1965
410 Fanburg B Finkel R M nd Martonosi, A.: The role of calcium in the mechanism of relaxation of ardiac muscle, J Biol Chem 239:2298, 1964
411 Fleckenstein A, Döring, H J and Kammermeier H. Experimental heart ... to inhibition of utilization of high-energy phosphates, Symposium on the coronary circulation and energetics of the myocardium Milan, 1966, Basel/New York ... S Karger p. 220.
411A. Kaufmann R and Fleckenstein, A. ... kompet tive elektro-mechanische Entkopelung durch N++ und Ca++ ... Warmblutermyokard, Pflügers Arch ... iol. 282:290, 1965
411B Hong C. R Effect of catecholamines ... on the utilization of calcium in cardiac actomyosin systems, in Symposium on ... gestiv circulatory failure, Berlin, ... to be published by Springer Verlag
412. Gertz, E. W Hess, M L, Lain, R F and Briggs, F N Activity of the vesic... calcium pump the spontaneously ... heart lung preparation Circulation Res 20:477 1967
413 Zimmerma A N E Daems, W ... man W C Snyder J West E ... Durrer D Morphological changes of ... muscle caused by successive perfusion ... calcium-free and calcium-containing ... tions (calcium paradox) Cardiovasc Res 1:201 1967
414. Lee, K. F Ladinsky H., and Stuckey J H ... Decreased Ca++ uptake by sarcoplasmic reticulum after coronary artery occlusion for 60 and 90 minutes, Circulation Res 21:439 1967
415 Gergeley J Contractile proteins Ann Rev Biochem 35:691 1966.
416 Huxley H. F Muscular contraction, Am Heart J 58 777 1959
417 Perry S V and Cotterill, J The action of thiol reagents on the adenosine-triphosphatase activities of heavy meromyosin and L-myosin Biochem. J 96:221, 19...
418 Burton, P and Lowenstein, J M ... Isolation of a complex of heavy meromyosin and adenine nucleotide Biochem J 90: ... 1964
419 W rd P C. J Edwards, C., and Benson E. S Relation bet een adenosine triphosphate activity and sarcomere length in stretched glycerol-extracted frog skeletal muscle Proc. N t Acad Sc. 53:1377, 19...
420 Tice L W and Barnett, R. J.: Fine structural localization of adenosinetriphosphatase activ ty in heart muscle myofibrils, J C... Biol. 15:401 1962.
421 H nson, J and Lowy J : The structure of actin filament and the origin of the ... periodicity in the I- bstance of vertebrate striated muscle Proc. Roy Soc. series ... 160:449 1964
422. Carney J A and Brown, A. L., J ... cardiac myosin lectron microscope ... servations, Circulation Res 17:135, 19...
423 Mueller H F anzen, J Rice R V Olson, R. E. Characterization of card...

myosin from the dog, J Biol. Chem. 239 1447 1964.
24. Gergeley J and Fial l, R. M Studies on cardiac myofibrillar adenosine triphosphatase, J Biol. Chem 236 1455, 1961
25. Kay C M and Green, W A.: Physicochemical and enzymatic studies on cardiac myosin A, Circulation Res (Suppl. II) 15:38 1964
426 Luchi, R. J Studies on canine cardiac myosin ATPase activity J Clin Invest. 44 1072 1965 (abstr.)
427 Szent-György A. Chemistry of muscular contraction, New York, 1947 Academic Press, Inc.
428 Taeschler M., and Bing R J Some properties of contractile proteins as studied on extracted heart muscle preparation, Circulation Res 1 129 1953
429 Davies, R. E Bioenergetics of muscular contractions, Chance B Estabrook, R W and Williamson, J R editors Control of energy metabolism New York, 1965 Academic Press Inc p 383.
430 Davies, R. E A molecular theory of muscle contraction calcium-dependent contractions with hydrogen-bond formation plus ATP dependent extensions of part of the myosin-actin cross-bridges, Nature 199 1068, 1963
431 Ebashi, S Iwakura, H Nakajima, H Nakamura, R and Ooi, Y New structural proteins from dog heart and chicken gizzard, Biochem Ztschr 345:201 1966
432. Mahirad, A., and Hegyi, G The role of Ca^{++} in the adenosine triphosphatase activity of myofibrils, Biochim. Biophys Acta 103:341 1965
433 Levy H M and Fleischer M Studies on the superprecipitation of actomyosin suspensions as measured by the change in turbidity I Effects of adenosine triphosphate concentration and temperature Biochim. Biophys Acta 100:471 1965
434 Kako, K and Bing R. J Contractility of actomyosin bands prepared from normal and failing human hearts, J Clin Invest. 37:465 1958.
435 Olson, L. E., Ellenbogen, E and Iyengar R Cardiac myosin and congestive heart failure in the dog, Circulation 24:471 1961
436. Davis, J O Trapasso, M and Yankopoulos, N A. Studies of actomyosin from cardiac muscle of dogs with experimental congestive heart failure Circulation Res 6:57 1959
437 Conway G F and Roberts, J L Comparison of molecular weight of myosin from normal and failing dog hearts, Am J Physiol. 208:343 1965.
438 Sonnenblick, E. H Spotnitz, H. M and Spiro, D Role of the sarcomere in ventricular function and the mechanism of heart failure, Circulation Res (Suppl II) 15 70, 1964
439 Chandler B M Sonnenblick E H Spann, J F J and Pool, P E. Association of depressed myofibrillar adenosine triphosphatase and reduced contractility in experimental heart failure, Circulation Res. 21 17 1967
440 Alpert, N R. and Gordon, M S. Myofibrillar adenosine triphosphatase activity in congestive heart failure Am. J Physiol. 202:940 1962.
441 Mommaerts, W F H M and Langer G A Fundamental concepts of cardiac dynamics and energetics, Ann. Rev Med 14:261 1963
442. Chidsey C. A Kaiser G A and Braunwald F Biosynthesis of norepinephrine in isolated canine heart, Science 139:828, 1963
443 Wurtman, R. J Catecholamines, New England J Med. 273:637 693 and 746, 1965.
444 Spector S Sjoerdsma, A., Zaltzman Nirenberg, P Levitt M and Udenfriend, S. Norepinephrine synthesis from tyrosine-C^{14} in isolated perfused guinea pig heart, Science 139 1299 1963
445 Kopin I J and Gordon, E. K Origin of norepinephrine in the heart, Nature 199 1289 1963
446 Nagatsu T Levitt M., and Udenfriend, S Tyrosine hydroxylase Initial step in norepinephrine biosynthesis, J Biol. Chem. 239:2910, 1964
447 Levitt, M Spector S., Sjoerdsma, A., and Udenfriend, S. Elucidation of the rate limiting step in norepinephrine biosynthesis in the perfused guinea-pig heart, J Pharmacol. & Exper Therap. 148 1 1965
448 Spector S Sjoerdsma, A., and Udenfriend, S Blockade of endogenous norepinephrine synthesis by alpha-methyl tyrosine, In hibitor of tyrosine hydroxylase, J Pharmacol & Exper Therap 14 :86, 1965.
449 Udenfriend, S Biosynthesis and release of catecholamines, von Euler U S Rosell, S and Uvnas, B editors Mechanisms of release of biogenic amines, Oxford, 1966 Pergamon Press, Inc p 103
450 Stromblad, B C R Effects of meal on adrenaline and noradrenaline content of some cat tissues, Proc Soc Exper Biol. & Med. 108:345 1961
451 Axelrod, J Formation, metabolism, uptake and release of noradrenaline and adrenaline Varley H and Gowenlock, A H editors The clinical chemistry of monoamines, Amsterdam, 1963 Elsevier Publishing Company p 5
452 Anden, N F Magnusson, T and Waldeck, B Correlation between noradrenaline uptake and adrenergic nerve function after reserpine treatment Life Sci 3 19 1964
453 Dengler H J Spiegel, H E., and Titus, E O Uptake of tritium-labelled norepinephrine in brain and other tissues of cat in vitro, Science 133 1072, 1961
454. Iversen, L. L. The uptake of noradrenaline by the isolated perfused rat heart, Brit. J Pharmacol 1:523 1963
455 Iversen, L. L. The uptake of adrenaline by the rat isolated heart, Brit. J Pharmacol 24:387 1965.

456. Wolfe, D. E., and Potter, L. T. Localization of norepinephrine in the atrial myocardium, Anat. Rec. 145:301, 1963.
457. Potter, L. T. and Axelrod, J. Subcellular localization of catecholamines in tissues of the rat, J. Pharmacol. & Exper. Therap. 142:291, 1963.
458. Braunwald, E., Chidsey, C. A., Harrison, D. C., Gaffney, T. E. and Kahler, R. C. Studies on the function of the adrenergic nerve ending in the heart, Circulation 28:958, 1963.
459. Kopin, I. J. Storage and metabolism of catecholamines: role of monoamine oxidase, Pharmacol. Rev. 16:179, 1964.
460. Bhagat, B. and Gilliam, J. J. Factors influencing the depletion of cardiac norepinephrine by tyramine, J. Pharmacol. & Exper. Therap. 153:191, 1966.
461. Gutman, Y. and Weil-Malherbe, H. Kinetics of catecholamine release by tyramine in rat heart, spleen, and uterus, Life Sci. 5:1293, 1966.
462. Black, J. W. and Stephenson, J. S. Pharmacology of a new adrenergic beta-receptor blocking compound (Nethalide), Lancet 2:311, 1962.
463. Dornhorst, A. C., and Robinson, B. F. Clinical pharmacology of a beta-adrenergic blocking agent (Nethalide), Lancet 2:314, 1962.
464. Gillis, C. N., Schneider, F. H., Van Orden, L. S. and Giarman, N. J. Biochemical and microfluorometric studies of norepinephrine redistribution accompanying sympathetic nerve stimulation, J. Pharmacol. & Exper. Therap. 151:46, 1966.
465. Crout, J. R., Creveling, C. R. and Udenfriend, S. Norepinephrine metabolism in rat brain and heart, J. Pharmacol. & Exper. Therap. 132:269, 1961.
466. Chidsey, C. A., Harrison, D. C. and Braunwald, E. Release of norepinephrine from the heart by vasoactive amines, Proc. Soc. Exper. Biol. & Med. 109:488, 1962.
467. Muscoll, E. Release of catecholamines from the heart, von Euler, U. S., Rosell, S., and Uvnas, B., editors: Mechanisms of release of biogenic amines, Oxford, 1966, Pergamon Press, Inc., p. 247.
468. Monroe, R. G., La Farge, W. J., Hammond, R. P. and Morgan, C. L. Norepinephrine release and left ventricular pressure in the isolated heart, Circulation Res. 19:774, 1966.
469. Wollenberger, A., and Shahab, L. Anoxia induced release of noradrenaline from the isolated perfused heart, Nature 207:88, 1965.
470. Braunwald, E., Harrison, D. C., and Chidsey, C. A. The heart as an endocrine organ, Am. J. Med. 36:1, 1964.
471. Levine, R. A. and Vogel, J. A. Cardiovascular and metabolic effects of adenosine 3', 5'-monophosphate in vivo, Nature 207:987, 1965.
472. Honig, C. R. Personal communication.
473. Honig, C. R. Influence of catecholamines and their analogs on ATP-induced contraction of cardiac myofibrils and myocardium, Tanz, R., Kavaler, F. and Roberts, J., editors: Factors influencing myocardial contractility, New York, 1967, Academic Press, Inc., p. 373.
474. Honig, C. R.: Depression of myocardium by catecholamine analogs: mechanism and in vivo significance, Am. J. Physiol. 214: 1968.
475. Klocke, F. J., Kaiser, G. A., Ross, J. Jr., and Braunwald, E.: Mechanism of increase of myocardial oxygen uptake produced by catecholamines, Am. J. Physiol. 209: 1965.
476. Welch, G. H. J., Braunwald, E., Case, R. B. and Sarnoff, S. J. The effect of mephentermine sulphate on myocardial oxygen consumption, myocardial efficiency and peripheral vascular resistance, Am. J. Med. 24:871, 1958.
477. Sonnenblick, E. H., Ross, J. J., Covell, J. W., Kaiser, G. A., and Braunwald, E. Velocity of contraction as a determinant of myocardial oxygen consumption, Am. J. Physiol. 209:919, 1965.
478. Jelinek, M., Kaye, M. P., Nigh, C. A. and Cooper, T. Alterations in chemical composition of canine heart after sympathetic denervation, Am. J. Physiol. 206:871,
479. Garland, P. B. and Randle, P. J.: An enzymatic assay for glycerol, Nature 196:987, 1962.
480. Rizack, M. A. Activation of an epinephrine-sensitive lipolytic activity from adipose tissue by adenosine 3', 5'-phosphate, J. Biol. Chem. 239:392, 1964.
481. Gold, M., Attar, H. J., Spitzer, J. J. and Scott, J. C.: Effect of norepinephrine on myocardial free fatty acid uptake and oxidation, Proc. Soc. Exper. Biol. & Med. 118:876, 1965.
482. Gousios, A., Felts, J. M. and Havel, R. Effects of catecholamines, glucose and changes of flow on the metabolism of free fatty acids by the myocardium, Metabolism 14:826, 1965.
483. Regan, T. J., Moschos, C. B., Oldewurtel, H. A., Weisse, A. and Asokan, S. K. Dominance of lipid metabolism in the myocardium under the influence of l-norepinephrine, J. Lab. & Clin. Med. 0:221, 1967.
484. Haugaard, N. and Hess, M. E.: Actions of autonomic drugs on phosphorylase activity and functions, Pharm. Rev. 17:27,
485. Hess, M. E., and Haugaard, N. The effect of epinephrine and aminophylline on phosphorylase activity of perfused contracting muscle, J. Pharmacol. & Exper. Therap. 122:169, 1958.
486. Mayer, S. E., and Moran, N. C.: Relation between pharmacologic augmentation of cardiac contractile force and the activation of myocardial glycogen phosphorylase, J. Pharmacol. & Exper. Therap. 129:271,
487. Kukovetz, W. R., Hess, M. E., Shanfeld,

J and Haugaard, N The action of ympa thomimetic amines on isometric contraction and phosphorylase activity of the isolated rat heart, J Pharmacol. & Exper Therap. 127 122, 1959
88 Haugaard, N Role of the phosphorylase enzymes in cardiac contraction proposed theory for the rhythmical production of energy in the heart, Nature 197 1072, 1963
89 Belford, J and Feinleib M C. Phosphorylase activity of heart muscle under various conditions affecting force of contraction J Pharmacol. & Exper Therap 127:257 1959
490 Hammermeister K. E Yunis, A A and Krebs, E. G. Studies on phosphorylase activation in the heart, J Biol. Chem 240 986, 1965
491 Mayer S E Cotten, M de V and Moran M. C Dissociation of the ugmentation of cardiac contractile force from the activation of myocardial phosphorylase by catecholamines, J Pharmacol & Exper Therap 139:275 1963.
492 Drummond, G I Valadares, R. J E nd Duncan, L. Effect of epinephrine on contractile tension and phosphor lase activation in t and dog heart Proc Soc Exper Biol. & Med. 11 :307 1964
493 Williamson, J R and Jamieson D Dissociation of the inotropic f om the glucogenolytic effect of epinephrine in he isolated rat heart, N tur 206:364 1965
494 Øye, I The action of adrenaline in cardiac muscle. Dissociation bet een phosphorylase activation and inotropic response, Acta physiol. scandina 65:251 1965
495 Chidsey C A Braunwald, E Morrow A. G., and Mason, D T Myocardial norepinephrine concentration in man, New England J Med. 269:653 1963
496 Chidsey C. A Kaiser G A Sonnenblick E. H., Spann, J A and Braunwald, E Cardiac norepinephrine stores in experimental heart failure in the dog, J Clin I vest 43:2386 1964
497 Chidsey C A Sonnenblick, E. H Morrow A G and Braunwald, E Norepinephrine stores and contractile force of papillary muscle from the f iling human heart, Circulation 33:43 1966.
498 Miyahara, M Catecholamine metabolism in heart muscle, Jap. Circ. J 26 1 1962
499 Fischer J E., Hor t, W D and Kopin I. J Norepinephrine metabolism in hypertrophied rat hearts, N ture 207:951 1965
500 Gaffney T F and Braunwald, F Importance of the adrenergic nervous ystem in the support of circulatory function in patients with congestiv heart failure Am J Med. 34:320 1963
501 Sandler G nd Wilson, G M The nature and prognosis of heart disease in thyrotoxicosis review of 150 patients treated with [131] Quart. J Med. 28:347 1959
502 Summers, V K., and Surtees, S. J Thyrotoxicosis and heart disease, Acta med Scandinav 169:661 1961
503 Likoff W B and Levine, S A. Thyrotoxicosis as sole cause of heart failure, Am. J M Sc 206:425 1943
504 Brewster W R., J Isaacs, J P Osgood, P F and King T L The hemodynamic and metabolic interrelationships in the activity of epinephrine, norepinephrine and the thyroid hormones, Circulation 13 1 1956.
505 Margolius, H S nd Gaffney T E. The effects of injected norepinephrine and sympathetic nerve stimulation in hypothyroid and h perthyroid dogs, J Pharmacol & Exper Therap 149:329 1965
506 Buccino, R. A Spann J F J Pool, P E., Sonnenblick E. H., and Braunwald E. Influence of the thyroid state on the intrinsic contractile properties and energy stores of the myocardium J Clin. Invest. 46 1669 1967
507 Goodkind M T The influence of thy oid hormone on myocardial metabolism of norepinephrine in the guinea pig, J Pharmacol & Exper Therap 154:531 1966
508 Gaffney T E Braunwald, E., and Kahler R L Effects of guanethidine on tri-iodoth onine-induced hyperthyroidism in man, New England J Med. 265 16, 1961
509 Wilson, W R Theilen, E. O and Fletcher F W Pharmacodynamic effects of beta adrenergic receptor blockade in patients with hyperthyroidism, J Clin. I est 43 1697 1964
510 Aoki, V S Wilson, W R., Theilen, E. O Lukensmeyer W W and Leaverton, P E. The effects of triiodothyronine on hemodynamic responses to epinephrine and norepinephrine in man, J Pharmacol & Exper Therap 157:62, 1967
511 Bressler R and Wittels, B The effect of thyroxine on lipid and carbohydrate metabolism in the heart, J Clin. Invest 45 1326 1966
512 Gold, M Scott, J C., and Spitzer J J Myocardial metabolism of free fatty acids in ontrol, hyperthyroid and hypothyroid dogs, Am J Physiol 213 239 1967
513 Ernster I Ikkos, D and Luft, R Enzymic activities of huma skeletal muscle mitochondria tool in clinical metabolic research, Natur 184 1851 1959
514 Hoch F L Thyrotoxicosis as a disease of mitochondria, New England J Med 266:446 and 498, 1962
515 Hoch, F L Mitochondria as a tart forge physiologic doses of thyroxine, Proc 5th Int. Thyroid Conf Abstract 116, 1965
516 Vitale, J J Nakamura, M and Hegsted, D M Oxidative phosphorylation, J Biol Chem. 228:573, 1957
517 Rachev R. R. Mechanism of hormonal action on oxidative phosphorylation in heart mitochondria, Fed. Proc. Translation Suppl 25 T874, 1966.
518 Wendt, V E., Stock, T B., Hayden, K. O

Bruce T A. Gudbjarnason S. and Bing R J The hemodynamics and cardiac metabolism in cardiomyopathies, M Clin. North America 46 1445 1962

519 Tata, J R Biological action of thyroid hormones at the cellular and molecular levels In Litwack G and Kritchevsky D editors Actions of hormones on molecular processes, New York 1964 Wiley & Sons, Inc p 58

520 Kadenbach B Effect of thyroid hormones on mitochondrial enzymes, Tager J M Papa, S Quagliariello E and Slater E C editor Regulation of metabolic processes in mitochondria Amsterdam 1966 Elsevier Publishing Company p 508.

521 Williams, R H Egana, E Robinson, P Asper S P nd Dutoit C Alterations in biologic oxidation in thyrotoxicosis I Thiamine metabolism Arch Int Med 2:353 1943

522 Wohl M C Levy H A Szutka, A and Maldia C P Iodine deficiency in hyperthyroidism Proc Soc Exper Biol. & Med. 105:523 1960

523 McBrien D J nd Hindle W Myxoedema and heart f 1 Lancet 1 1066 1963

524 Aber C J Noble R J Thompson C S and Jones F W Serum lactic dehydrogenase isoenzymes in myxoedema heart disease Brit Heart J 28:663 1966

525 Scott J C Bourdas, T A and Coll, M N The effect of experimental hypothyroidism on coronary blood flow and hemodynamic factors, Am J Cardiol. 8:690 1961

526 Den Bakker J B Sundermeyer J F Wendt V J Salhanes M Gudbjarnason S nd Bing R J Myocardial metabolism in a patient with Hashimoto thyroiditis nd hypothyroidism Am. J Med. 31:822 1961

527 Mezler P L Contractility of isolated heart from myxoedematous rats, Israel Med J 22:395 1963

528 Goodkind M J Fram D H and Roberts, M Effect of thyroid hormone on myocardial catecholamine content of the guinea pig Am J Physiol 201 1049 1961

529 Wurtman R J Kopin I J nd Axelrod, J Thyroid function and cardiac disposition of catecholamines Endocrinology 73:63 1963

530. Benforado J M nd Wiggins, L L Contractility heart rat and response t norepinephrine of isolated at myocardium following 131 induced hypothyroidism J Pharmacol & Exper Therap. 11 70 1965.

531 Courville C O nd Mason V R The heart in acromegaly Arch Int Med. 61 704 1938.

532 Hejtmancik M R Bradfield T Y J and Herrman, C R. Acromegaly nd the heart a clinical and pathological study Ann. Int Med. 34 1445 1951

533. Gordon D A., Hill, F M and Ezrin, C Acromegaly a review of 100 cases, Canad M A. J 87:1106, 1962.

534 Davidoff L. M: Studies in acromegaly. III The anamnesis and symptomatology in 100 cases, Endocrinology 10:461 1926

535 Balzer R., and McCullagh, E P Hypertension in acromegaly Am. J M Sc 237 449 1959

536. Hamwi, G J Skillman, T C, and Tufts J C. J Acromegaly Am. J Med. 29 1960.

537 Palagi, L Sonnino, S and Mosconi C L apparato cardiocircolatorio nell'acromegalia (studio su 29 casi), Policlinico (Prat.) 70:365 1963.

538. Bricaire H Chiche, P Acar J and Luton P Manifestations cardiovasculaires de l acromegalie Presse. Med. 70:531, 1962

539 Hackel, D B Goodale W T and Kleinerman, J Effect of thiamine deficiency myocardial metabolism in infant dogs Am. Heart J 46:883, 1953.

540. Huckabee W E. Nutritional heart disease Biochem, Clin. 1:37 1963

541 Raab, W and Supplee, C G. Cardiac adreno-sympathetic activity in vitamin deficiencies, Exper Med. & Surg 2:152 1944

542. Goodall M Studies of adrenaline and noradrenaline in mammalian heart and suprarenals, Acta physiol scandinav (Suppl 85) 24 1 1951

543 Brink A J Lochner A and Lewis C M Thiamine deficiency and beriberi heart disease South African M J 40:581 1966

544 Eliaser M J and Giansiracusa F J The heart and alcohol, California Med 84:204 1956.

545. Burch G. E and Walsh, J J Cardiac insufficiency in chronic alcoholism, Am J Cardiol. 6:864 1960.

546 Wendt, V E., Wu, C., Balcon, R Doty G. and Bing, R. J: Hemodynamic and metabolic effects of chronic alcoholism in man, Am. J Cardiol 15 175, 1965

547 Hibbs, R. G Ferrans, V J Black, W C Weilbaecher D G. Walsh, J J and Burch G. E. Alcoholic cardiomyopathy An electron microscopic study Am. Heart J 69 766 1965.

548. Burbridge, T N Hine C. H Elliott, H W nd Sutherland V C. The in vitro metabolism of ethanol by rat tissue slices, J Pharmacol & Exper Therap. 101:5, 1951.

549 Lindeneg, O Mellemgaard, K Fabricius J and Lundquist, F Myocardial metabolism of acetate lactate nd free fatty acids after ingestion of alcohol, Clin. Sc 27:427 1964

550. Haggard, H W Greenberg, L. A. Cohn L. H., and Rakieten, N J Studies on the absorption, distribution nd elimination of alcohol. IV The concentration of alcohol in the blood causing primary cardiac failure J Pharmacol. & Exper Therap. 1941

551 Regan T J Weisse A B Oldewurtel H. A., and Hellems, H K: The

somotic effects of ethanol and sucrose on the left ventricle J Clin Invest. 43 1289 1964 (abstr)

1. Ganz, V The acute effect of alcohol on the circulation and the oxygen metabolism of the heart, Am. Heart J 66:494 1963

1. Sw nepoel, A., Smythe, P M and Campbell, J A. H. The heart in kwashiorkor Am Heart J 6 1, 1964.

1. Mansford, K. R. L., and Ople, L. H Comparison of metabolic abnormalities in diabetes mellitus induced by streptozotocin or by alloxan Lancet 1:670 1968.

5. Read, J V O nd Berjak, P Dietary production of myocardial fibrosis in the rat, Am. Heart J 1:240, 1966

6. McKinney B nd Cra ford, M A Fibrosis in guinea pig heart produced by plantain diet, Lancet 2:880 1965

7 Crawford, M A. Endomyocardial fibrosis and carcinoidosis common denominator Am. Heart J 66:273, 1963

58 Roberts, W C and Sjoerdsma, A The cardiac disease associated ith the car noid syndrome (carcinoid heart disease) Am J Med 36:5 1964

59 Rosal, P Stevenson M Khakaar I and Bellet, S. Coronary arteriosclerosis induced in young dogs by prolonged intra-aortic infusions of serotonin, Circulation Res 9:436 1961

60. Walton, R P Walton, R P J and Thompson, W L Inotropic activity of catechol isomer and series of related compounds, J Pharmacol & Exper Therap 125:202, 1959

561 Spatz, M P thogenic studies of experimentally induced heart lesions and their relation to the carcinoid syndrome Lab Invest. 13:288, 1964

562. Thorson, A. H Hemodynamic changes during flush in carcinoidosis (The carcinoid syndrome) Am Heart J 52:444 1956

563 Oates, J A., Melmon, K Sjoerdsma, A Gillespie, L and Mason, D T Release of kinin peptide in the carcinoid syndrome, Lancet 1:514 1964.

564. Germeyer E. F and Spitzbarth, H Uber kreislaufwirkungen von s thetischen Bradykinin beim Menschen und beim schen Hund, Klin. Wchnschr 39 1227 1961

565. Tobin, J R., Driscoll, J F Lim M T Sutton, G C Szanto P B., and Gunnar R. M Primary myocardial disease and alcoholism the clinical ma ifestation nd course of the disease in selected population of patients observed for three or more years, Circulation 35 754 1967

566. Beachiaol, A. B and Schlesinger P Beri-beri heart disease, Am H art J 46:245 1953

56 Sayen, J J Sheldon, W F Peirce C nd Kuo, P T Polagraphic oxygen, epicardial electrocardiogram and muscle contraction in experimental acute egional ischemia of left entricle, Circulation Res. 6 779 1958

568. Jennings, R. B., Baum, J H nd Herdson, P B Fine structural changes in myocardial ischemic injury Arch Path. 79 135 1965

569 Bryant, R E Thomas, W A. and O'Neal, R. M An electron microscopic tudy of myocardial ischemia in the rat, Circulation Res. 6:699 1958.

570 Russell, R A Crafoord, J nd Harris, A. S. Changes in myocardial composition after coronary artery ligation Am J Physiol 200:995 1961

571 Harris, A. S., Bisteni, A Russell, R A., Brigham, J C., and Firestone, J E. Excitatory factors in ventricular tachycardia resulting from myocardial ischemia, Science 119:200 1954

572. Lamprecht, W The effect of acute and chronic ischemia on myocardial contractility James, T N and Keyes, J W editors The etiology of myocardial infarction, Boston, 1963, Little Brown & Company p. 393

573 Kattenbach J P nd Jennings, R. B Metabolism of ischemic cardiac muscle Circulation Res. 8:207 1960

574 Jennings, R B Sommers, H Smyth, G., Flack, H and Linn, H. Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog, Arch. Path. 70:68, 1960

575 Lancet, Editorial P opr nolol and myocardial infarction Lancet 2:950, 1966

576 Godbjarnason, S DeSchryver C and Chiba, C Protein metabolism in the heart following myocardial infarction, J Lab & Clin Med 62:880 1963

577 Fetisova, T V and Zabolotnyak, I P Changes in heart muscle and liver proteins in experimental myocardial infarction, Fed Proc T anslation Suppl. 24 T860, 1965

578 Mittra, B Potassium, glucose and insulin in the treatment of myocardial infarction, Lancet 2:607 1965

579 Mittra, B Potassium, glucose and insulin in treatment of heart block after myocardial infarction, Lancet 2 1438 1966.

580 Regan, T J Harman, M A Lehan, P H Burke W M nd Oldewurtel, H A. Ventricular arrhythmias and K transfer during myocardial ischemia and intervention with procaine amide insulin or glucose solution, J Clin Invest 46 1657 1967

581 MacLeod, D P and Daniel, E. E. Influence of glucose on the transmembrane action potential of anoxic papillary muscle J Gen Physiol 48:887 1965

58 Krall, A R Wagner M C and Gozansky D M Potassium ion stimulation of oxidative phosphorylation by brain mitochondria, Biochem. Biophys. Res. Commun. 16 77 1964

583 Kimmich G. A and Rasmussen, H Inhibition of mitochondrial respiration by loss of intramitochondrial K Biochim Biophys Acta 131:413 1967

584 McKeune, J Taylor S. H Fleniey D C McDonald, A H Staunton, H. P and Donald K. W Circulatory and respiratory

studies in myocardial infarction and cardiogenic shock, Lancet 2:825 1964.

585 Hall, I H. Effectiveness of THAM in preventing cellular damage resulting from oxygen lack, Proc. Soc Exper Biol. & Med. 122:1240, 1966.

586. Reynolds, R. C and Haugaard, N The effect of variations of pH upon the activation of phosphorylase by epinephrine I perfused contracting heart, liver slices and skeletal muscle, J Pharmacol. & Exper Therap 156:417 1967

587 Daw J C and Berne, R. M Effect of sympathectomy on cardiac UDPG-glycogen transferase activity in the cat, Am. J Physiol 213 1480, 1967

588. Yamamoto, M Masanobu and Drummond G I Monoglyceride-hydrolyzing activity of rat myocardium Am. J Physiol. 213 1365 1967

589 Schreiber S S Oratz, M and Rothschild M A Effect of acute overload on protein synthesis in cardiac muscle microsomes, Am. J Physiol 213 1552 1967

590. Wollenberger A., and Krause, E.G. K... bolic control characteristics of the ... ischemic myocardium, Am. J Cardi... press.

591 Reeves, R. B.: Enzyme activities ... mal rates of glycolysis in ... cardium Am. J Physiol. 21... 19...

592 Gercken G., and Schlette, U. Met... status of the heart in acute insufficiency ... to 1 fluoro-2 4-dinitrobenzene, Experi... 24 17 1968.

593 Katz, A. M.: Absence of direct action ... norepinephrine on cardiac myos... cardiac actomyosin, Am J Physiol 21... 1967

594. Luchi, R. J and Kritcher E. M: ... effects on cardiac myosin adenosine tri... phatase activity J Pharmacol & Exp Therap. 158:540, 1967

595 Gudbjarnason, S. Fenton, J C, ... and Bing R. J: Stimulation of ... processes following experimental myocardial infarction, Arch. Int. Med. 11..., 19...

Fundamentals of clinical cardiology

Coronary artery disease and major conduction disturbances

A pathologic study designed to correlate vascular and conduction system abnormalities with electrocardiogram

James R. Harper M.D
Alexander Harley M B M R C.P **
Donald B Hackel M.D ***
E. Harvey Estes Jr M.D ****
Durham N C

Coronary artery disease and myocardial infarction are frequently associated with major conduction abnormalities. The incidence of such complications with acute infarction ranges from 6 to 15 per cent for bundle branch block[1-3] and from 2 to 5 per cent for complete heart block.[4-8] Slightly higher incidences are noted with the use of continuous monitoring systems. There are marked variations in the clinical course of these conduction disturbances. When occurring with acute infarction complete heart block has been associated with mortality rates of 40 to 100 per cent.[4-8] However both complete heart block and bundle branch block may sometimes be transient phenomena[8,1] attributable to temporary ischemia or edema of the conduction tissue, and not necessarily associated with high mortality rates. In addition it is stated that chronic forms of major conduction disturbances are rarely sequels of acute myocardial infarction[11] but are usually related to chronic nonocclusive coronary artery disease and hypertension.[12] These observations serve to emphasize the enormous variability in the clinical setting of major conduction disturbances associated with coronary artery disease.

The pathology of the cardiac conduction system in coronary artery disease has been the subject of several excellent reviews.[13,14,15] The methods of Lev and associates, Lenègre and Chevalier[17] and James and Burch[8,1] have contributed greatly to our knowledge of the anatomy and vascular supply of the region of the upper interven-

From the Departments of Medicine and Pathology Duke University Medical Center Durham, N. C
Dr Harper was supported by United States Public Health Service Training Grant No HE-32,354-01; Dr Harley was supported by United States Public Health Service Training Grant No. HE-05340 Dr Hackel was supported by National Institutes of Health Grant No. PH 43-67-1440, National Institutes of Health Research Grant HE-03373, and United States Public Health Service Career Research Award N HE-K6-14,108. This work also received support from the following grants National Institutes of Health Training Grant K HE-05736, and grant from the American Medical Association Committee for Research on Tobacco and Health (Dr Estes)

*Fellow in Medicine
**Fellow in Medicine
***Professor of Pathology
****Professor of Medicine.

tricular septum where the major structures of the conduction system lie. Both Lev and Unger[9] and Lenègre[14] have demonstrated by their special techniques of study that major defects in atrioventricular conduction are well correlated with pathologic lesions. Despite excellent histologic correlation of conduction system lesions with electrocardiographic abnormalities, few attempts have been made to interrelate vascular pathology with these lesions. The vascular anatomy of the upper septum has been described by earlier workers[19,21] and more recently expanded by James.[22] The contribution of major coronary vessels to the blood supply of the various portions of the cardiac conduction pathways has also been emphasized.[13,23] From these works a reasonable assumption has been that specific conduction abnormalities might be associated with specific vascular lesions but this hypothesis has not been tested in previous studies.

The present study was confined to eight cases. Each case presented an acute or chronic major conduction disturbance documented by electrocardiogram (ECG). Postmortem examination was performed in each case and two techniques of pathologic study were integrated, one designed to demonstrate vascular anatomy and the other allowing detailed study of the conduction system. An attempt was made to examine the question of association of specific vascular lesions and conduction abnormalities in coronary artery disease with or without actual myocardial infarction.

Materials and methods

During the past three years, 185 hearts have been randomly selected for injection studies of their coronary vascular system. Of these specimens, 76 warranted additional study of their conduction system because of some particular clinical problem. From this latter group eight cases were selected retrospectively for inclusion in the present study. The criteria for selection included documentation of coronary artery disease at postmortem examination and a conduction disturbance of a type suggesting involvement of the major pathways of conduction tissue. Although the actual existence of a myocard[ial in-] farction either old or recent was no[t con-] sidered as a criterion for selection... of the eight cases revealed patholo[gic] evidence of myocardial damage ... infarction. The duration of the conduc[tion] disturbance, or its temporal relation to the clinical history of myocardial ... tion were not considered in ...

A modification of the Schlesinger ... tion technique described else... the text,[24] was used to study selected ... coming to autopsy. Following injection ... the coronary arteries with the radiopaque mixture the heart was allowed to fi[x in] 20 per cent formalin and an x-ray of ... whole specimen was taken (Fig. 1 ... detailed gross pathologic examination ... performed, specifically noting vas... lesions and the vascular origin of the ... supply to the sinoatrial node and atrio[ven-] tricular node regions. In addition, gr[oss] visible myocardial lesions were recor[ded] and appropriate sections were taken ... microscopic examination. Following ... gross examination the free walls of ... right and left ventricles were remo[ved] and a lateral view x-ray of the inter[ven-] tricular septum was taken (Fig. 1), ... cording to the method of Lev and as[soci-] ates,[16] the block of tissue containing ... AV node and AV conduction tissue ... then removed from the upper inter[ven-] tricular septum (outlined in Fig. 1) ... microradiograph was taken of this ... in order to concentrate on vessels in ... region of the cardiac conduction tis[sue]. An enlargement was made of the x-... of the latter block of tissue and was pr... on heavy matte paper for later refer[ence].

The block of tissue containing the ... cardiac conduction structures diagr[am-] matically represented in Fig. 3 ... subjected to serial sectioning at 7 mic... intervals. Every thirtieth section ... mounted on a glass slide and stained ... hematoxylin and eosin. The rema[ining] sections were placed on 35 or ... plastic film strips according to the te[ch-] nique described by Lickett and Sorre... and were stained with Masson's trich[rome] stain. The study of the serial sections ... facilitated by the use of a projection ... tem designed for military map rea[ding]



Fig. 1 X-ray of intact postmortem cardiac specimen showing injection of the coronary vessels with radio-opaque barium-gelatin mixture. Views of this type assist in confirming gross pathologic coronary lesions, and in documenting coronary vascular anatomy.



Fig. 2 Right lateral view of the interventricular septum from the case shown in Fig. 1. The free walls of the right and left ventricles have been removed. The posterior descending artery (*PDA*) is to the left. The artery that looks like a fish-hook is the atrioventricular nodal artery (*AVNA*). The left anterior descending coronary vessel (*LAD*) is seen on the right. *RCA* indicates right coronary artery. The white square outlines the approximate area removed for further study of the major structures of conduction tissue (see Fig. 4).

which allowed rapid forward and backward scanning. Several thousand serial sections could be scanned in a continuous manner with individual sections still being available for microscopic examination. The projection system produced an image at a magnification of 20 times the size of the object, and the image was projected on the ground glass screen of the apparatus.

By integrating the two proceeding methods of studying the upper interventricular septum several advantages were realized. The radiographic reproductions provided a framework or "roadmap" which could be used to identify specific vascular structures in the serial sections. Once specific structures such as vessel bifurcations or particular vascular turns were accurately identified the conduction tissue present in a particular serial section could be represented in appropriate dimensions and position relative to the identifiable vascular structure. This allowed a reasonably accurate reconstruction of the atrioventricular node, common bundle, and early portions of the major bundle branches to be portrayed on the enlarged reproduction of the vascular radiograph. The location of pathologic lesions identified in the serial sections could then be viewed in direct relation to the surrounding vascular anatomy of the upper interventricular septum.

Results

Table I summarizes the essential data on the eight cases selected for study. Included in the entire group were three cases of right bundle branch block, three cases of left bundle branch block, one case of complete heart block, and one case of

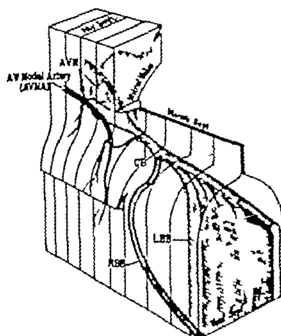


Fig 3 Diag[illegible] representation of the major tru[illegible] d[illegible] conduction tissue found [illegible] the p[illegible] ven[illegible] tricular septum and their general [illegible] ship [illegible] topographical anatomy [illegible] James T N Morphology of the h[illegible] atrioventricular node with remarks per[illegible] electrophysiology Am Heart J 62 756 1961

varying first and second degree block a right bundle branch block pattern [illegible] terminally evolved into complete atrioventricular dissociation. Brief case histories are presented in the Appendix.

Sex and age There were five men and three women in the group. All cases were in their seventh or eighth decade of life with the exception of patient 8 who reported to have suffered his first myocardial infarction at the age of 35 and was 51 years of age at the time of his death

Duration of conduction disturbance The duration of the conduction disturbance varied from a period of three days to [illegible] years In two instances both left bundle branch block the conduction disturbance were felt to be of acute onset and were associated with recent chest pain compatible with myocardial infarction In a third instance patient 8 a significant conduction disturbance had been present for [illegible] years, but the terminal course was marked by changing rhythm disturbances and ultimate atrioventricular dissociation associated with acute myocardial infarction

Clinical features Only one of the eight patients had documented systemic arterial hypertension There were two cases of

Table 1

Patient No.	Age	Sex	ECG	Duration (yr)	Pathology: Vascular* LAD	LCA	RCA	AVNA	Septal branches	Conduction tissue† AVN	CB	RBB	LBB
1	72	M	RBBB‡	Unknown	+++	0	0	0	++	0	+	+++	+
2	73	M	RBBB	2	+++	++	+++	0	++	0	0	+++	[illegible]
3	64	F	RBBB	10	+++	+++	+++	0	+	0	0	0	0
4	69	F	LBBB	Acute	+	++	Th	+++	+++	++	++	0	+
5	69	F	LBBB	Acute	+++	+++	+++	+++	0	0	0	0	
6	[illegible]	M	LBBB	4	0	0	++	0	0	0	0	0	
7	67	M	CHB	4	+++	0	0	0	0	0	++	+++	
8	51	M	AV	5	+++	++	+++	+	++	0	0	++	++

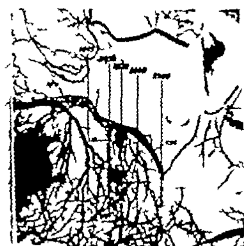
*% vascular (per cent narrowing 0 normal + 0-25 ++ 25-50 +++ 50-100% Th, acute thrombus
†Conduction tissue (degree of involvement) 0 normal + mild ++ moderate +++ marked; ++++ complete [illegible]
‡Right bundle branch block (RBBB) left bundle branch block (LBBB) complete heart block (CHB) atrio[illegible]
(AV Diss) left circumflex artery (LCA) right coronary artery (RCA), left anterior descending coronary artery [illegible] atrioventricular nodal artery (AVNA)

diabetes mellitus. Acute infarction was felt to be the immediate cause of death in four patients. One patient died with terminal renal failure, three died with progressive congestive heart failure, and one of these developed septic shock as a complication of insertion of a transvenous pacemaker.

Pathologic findings. The pathologic findings were divided into two major categories: those related to vascular structures, and those related to conduction tissue abnormalities. Vascular pathology was graded from 0 to 3+, depending on the degree of lumen encroachment. In one instance (Patient 4) an acute thrombus of the right coronary artery was found. In addition to grading pathologic lesions found grossly in the three main coronary vessels, the state of the AV nodal artery was also noted. Likewise an appraisal of the septal vessels was made by microscopic examination of the serial sections and by examining the vascular radiographs.

In evaluating conduction tissue pathology, a *grading* system of *0 to 4+* was arbitrarily chosen to represent normal, mild, moderate, marked, and complete involvement. In Table I no distinction is made between acute necrosis and fibrosis.

RIGHT BUNDLE BRANCH BLOCK. In the three cases with right bundle branch block two had moderate to severe disease of all three major coronary vessels. In one of the three cases severe disease of only one major coronary vessel, the left anterior descending artery, was noted. The case which involved only the left anterior descending artery revealed the most extensive fibrotic disease of the conduction tissue. In this instance, there was additional involvement of both the common bundle and left bundle but to a lesser degree than the right bundle. Evaluation of septal vascular pathology revealed atherosclerotic disease of a mild to moderate degree in all three cases of right bundle branch block, but most severe in Case 1 which had the most extensive conduction tissue involvement. In Case 3, whose right bundle branch block was documented 10 years earlier, *no pathologic lesions* were found in the conduction tissue to account for the electrocardiographic abnormality. This was *true despite severe narrowing* of all three major coronary vessels. It is perhaps significant to note that this pa-



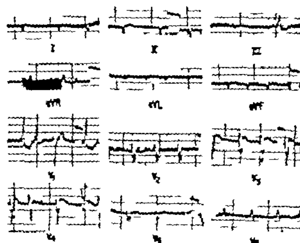


Fig. 4. X-ray of the isolated block of tissue outlined in Fig. . An outline of the conduction tissue is superimposed to show its relationship to the surrounding vascular supply. The regions of the atrioventricular node (AVN), common bundle (*CB*), left bundle branch fiber (*LBB*) and the right bundle branch (*RBB*) are labeled. The numbered vertical lines represent the plane of serial sections which correspond to those seen in Fig. 3. The shaded area of the right bundle branch represent areas in which fibrosis was noted in serial sections. Also, ECG from Case 2 showing the right bundle branch block pattern.

tient's septal vessels were the least involved in pathologic atherosclerotic narrowing

Fig 4 shows the electrocardiogram and diagrammatic reproduction of the conduction tissue structures in relation to the blood supply found in Case 2 Fig 5 shows the corresponding numbered serial sections and the anatomy demonstrated at each level of the cut section

LEFT BUNDLE BRANCH BLOCK. The five cases representing left bundle branch block exemplify the broad spectrum of coronary vascular disease that was noted in this study Case 4 was the only one of eight cases which represented an acute thrombosis demonstrable at postmortem examination. The main left coronary artery was occluded near its origin and only mild to moderate athero-



Fig 5 Pathologic sections from Case 2, which were identified by the numbered vertical lines in Fig 4. A (Section 1643) shows the normal common bundle characteristically surrounded by fibrous tissue of the central fibrous body. B (Section 2030) shows the early bifurcation of the common bundle into right and left bundle branches. C (Section 2339) shows the area of fibrosis of the right bundle after penetrating into the interventricular septum

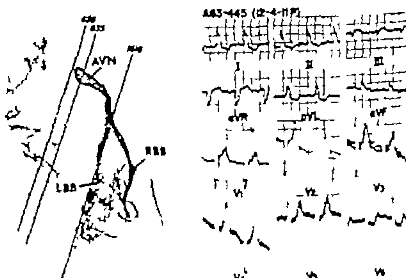


Fig 4 X-ray of the isolated block of tissue from the upper interventricular septum of Case 4. The lightly stippled area outlines the area of acute necrosis which is seen to involve the lower portion of the atrioventricular node and the origin of the left bundle fibers. Also, ECG from Case 4 demonstrating the left bundle branch block conduction abnormality

sclerotic disease was noted in the two remaining major coronary vessels. Conduction system pathology was also noted to be more extensive and acute in this case than in the other two cases representing left bundle branch block (Fig. 6). The inferior portion of the atrioventricular node and the entire left bundle were involved in an extensive acute infarction predominantly of the left side of the interventricular septum. It is interesting to note in more detail some of the vascular pathology in Case 4. The fresh occlusion of the right coronary artery prevented filling of the AV nodal artery, which was markedly sclerotic on pathologic section. The diagrammatic sketch of the conduction tissue (Fig. 6) shows the relationship of the conduction tissue abnormalities to the vascular pathology. The acute myocardial infarction was noted in the region in which few major vascular structures were filled with injection material (compare with vascular structures in Fig. 4). The sparing of the superior portion of the atrioventricular node is of particular interest in view of the close proximity of this structure to atrial vessels which are adequately filled. It is also of interest that in this case the artery supplying the major portion of the atria and the sinoatrial node arose from the left coronary system rather than from the right coronary artery which was occluded by the acute thrombus.

The two remaining examples of left bundle branch block were not associated with acute thrombosis of a major coronary vessel, though one of the cases, Case 5, was believed to be of recent onset. Case 5 had extensive disease of all three major coronary vessels and the AV nodal artery. Gross pathologic examination revealed extensive old and new myocardial infarction predominantly involving the anterior septum, but also involving the anterior and posterior ventricular walls. In spite of this extensive gross and microscopic vascular and myocardial pathology, the conduction tissue was only moderately involved, the left bundle being involved in a discrete fibrotic process near its origin. In direct contrast, Case 6, the third example of left bundle branch block, revealed only 25 to 50 per cent narrowing of the right coronary artery, but a discrete fibrotic lesion at the origin of the left bundle branch fibers was noted, and was slightly more pronounced than in Case 5. There was no gross evidence of myocardial infarction in Case 6, and only scattered fibrotic lesions throughout the myocardium were seen on microscopic examination.

COMPLETE HEART BLOCK. The two cases representing examples of complete heart block were quite different in the evolution of the conduction disturbance and were equally divergent in pathologic findings. Case 7, in whom conduction abnormality had been noted four years prior to his death, had marked involvement of only one major coronary artery, the left anterior descending. There was evidence of extensive old anterior myocardial infarction. The septal vessels were not significantly involved with atherosclerotic disease. The left bundle branch fibers were virtually replaced by dense fibrous tissue, and both the right bundle branch and common bundle were similarly affected though to a lesser degree.

Case 8 had extensive disease of all three major coronary vessels and moderate atherosclerotic disease of the septal branches. There was considerable fibrosis of the interventricular septum which virtually engulfed the fibers of the left bundle but involved the right bundle branch to a lesser degree. There was evidence of extensive old anterior myocardial infarction, involving the septum and anterior wall of the left ventricle with an aneurysmal dilatation of the left ventricle.

Discussion

Early workers[20-24] and more recently James[22] have contributed greatly to our knowledge of blood supply to the upper interventricular septum and the specialized conduction tissue. Mahaim[24] was among the first to emphasize the importance of vascular supply to the heart's specialized conduction tissue and its relationship to coronary vascular syndromes. Lev and Unger[23] and James[22] have more recently emphasized these anatomic relationships in their writings. The implications have been that in the presence of coronary artery

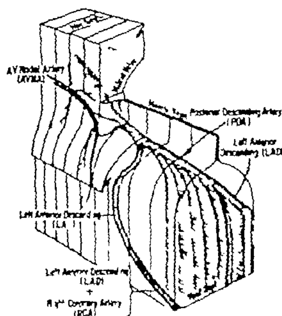


Fig 7 Diagrammatic representation of the cardiac conduction tissue demonstrating the anatomic contribution of blood supply from the atrioventricular nodal artery (AVNA), left anterior descending artery (LAD), right coronary artery (RCA) and the posterior descending artery (PDA)

line second more specifically in occlusive coronary artery disease the occurrence of particular disturbances in conduction should be correlated with specific vascular lesions

A diagrammatic representation of the anatomy of the blood supply to specialized conduction tissue is depicted in Fig 7

The literature regarding the correlation of vascular and conduction tissue pathology is both scant and confusing On the one hand both clinicians and pathologists have stated that coronary artery disease is a rare cause of persistent atrioventricular block.[11,37] However Lenègre[33] has pointed out that in the case of bilateral bundle branch block coronary artery disease is incriminated in approximately 50 per cent of the cases Despite much speculation about the relationship of coronary artery disease to conduction disturbances, there have been no studies to date which have examined in detail the vascular anatomy of cases where conduction disturbances and coronary artery disease coexisted.

In our series we were able to confirm in seven of eight cases that there was histologic conduction tissue lesion which correlated with the patient's electrocardiographic abnormality No attempt was made to determine the amount of histologic abnormality necessary to produce electrocardiographic changes, but as noted in our summary of results (Table II) in Cases 1 and 4 there was evidence of more extensive histologic damage than would have been predicted from the ECG.

Except in the case of the acute coronary thrombosis (Case 4) there was poor correlation between vascular disease involving any single major vessel or any particular combination of coronary vessels and a specific conduction abnormality For instance in Case 1 only one major vessel was involved with atherosclerosis yet extensive disease of the conduction system was noted On the other hand, Case 3 was found to have extensive large vessel disease and the identical conduction disturbance as in Case 1 yet no anatomic conduction tissue defect was found.

The conduction abnormalities of short duration appeared to correlate more closely with vascular pathology However this may be due to the small number of cases such as Case 4 in which acute vascular occlusion was noted Case 5 which also had a conduction disturbance of recent onset failed to demonstrate any specific vascular lesion which might be held responsible for the conduction tissue pathology

Despite a negative correlation between specific vascular lesions and conduction abnormalities noted by ECG several observations can be made In this series of patients it is apparent that major conduction abnormalities are accompanied by the same broad spectrum of vascular pathology that has been noted in coronary artery disease in general At one end of the spectrum is acute occlusive vascular disease which is expected to give the highest degree of correlation between specific vascular lesions and specific conduction tissue lesions The other end of the spectrum is characterized by chronic coronary vascular disease subject to many hemodynamic variables of an undefined nature

presents a very low degree of correlation between a specific vascular lesion and major conduction disturbances. The reason for this variability is judged to be related to the existence of collateral circulation. In acute coronary occlusion tissue necrosis and edema are frequently found involving an area of undeveloped collateral circulation. This may indeed produce a significant correlation between the involved vessel and a specific conduction tissue lesion. In our study this particular pathologic feature was noted in only one of eight instances. Even in acute occlusion, however rich preexisting anastomotic channels in the upper interventricular septum would make this an unpredictable event. On the other hand, chronic coronary artery disease gives a low incidence of correlation between specific vascular lesions and specific conduction disturbances. Though localized fibrosis of conduction tissue pathways may be observed, the extensive ingrowth of collateral vessels makes it impossible to delineate a specific vascular lesion as the cause of the diseased conduction tissue.

The over-all variability of pathology in association with coronary artery disease and myocardial infarction is adequate to explain the marked variation in the clinical courses of these patients. The high mortality rates associated with conduction disturbances complicating acute myocardial infarction[1-11] undoubtedly account in part for the observation that chronic disturbances are rarely seen in this setting.[25] However with the improvement in management of acute infarctions by the use of artificial pacing the mortality rates are already on the decline,[26] and the chronic conduction disturbances will probably be more frequently observed. Further studies such as this one may shed more light on these correlations.

Summary

A technique for correlating vascular anatomy with conduction tissue structures in the human heart has been described. This technique was used to study eight selected cases of coronary artery disease who demonstrated major conduction disturbances by ECG.

The following conclusions are reached

1 There is good correlation between histologic changes in the major pathways of the conduction system and demonstrable electrocardiographic abnormalities.

2 There is poor correlation between specific vascular pathology and histologic changes in the major conduction pathways except when related to fresh vascular occlusive disease.

3 The development of collateral circulation in the upper interventricular septum is the one anatomic feature which appears to govern the relationship between vascular and conduction tissue pathology

4 The broad spectrum of pathologic processes in coronary artery disease associated with major conduction disturbances is felt to account for the marked variability in the clinical setting and course of these cases

Appendix

Case 1 J F M (D U No. E3 3 952) was 72 year-old Negro man with a documented 10 year history of hypertension There was history of recent chest pain, but no definite history suggesting myocardial infarction. He was initially seen in 1956 for symptoms of prostatic hypertrophy but was not seen again until his terminal admission in 1965 His ECG revealed a right bundle branch block with evidence of old anterior and diaphragmatic infarction The patient died in terminal renal failure.

Postmortem examination of the heart revealed 90 per cent occlusion of primary radicle of the left anterior descending coronary artery extending 1 cm in length There was no gross or microscopic evidence of myocardial infarction, though there were scattered areas of myocardial fibrosis.

Case 2 A L T (D U No. F8 4 458) was 75-year-old Caucasian man, initially seen in November 1962 because of congestive heart failure. His heart was in atrial fibrillation, which was converted to sinus rhythm with digitalis and quinidine, but in July 1963 atrial fibrillation recurred with frequent premature ventricular contractions. In November 1965 he was hospitalized with congestive failure, atrial fibrillation, frequent ventricular premature beats and conduction defect of the right bundle branch block type During this hospitalization, he complained of severe right shoulder pain and was found to be hypotensive. An ECG was suggestive of acute infarction. The patient rapidly developed ventricular fibrillation and died.

Postmortem examination of the heart revealed heavy calcification of the orifices of both the right and left coronary arteries. The right coronary artery and anterior descending artery were 80 per cent occluded by this calcification No recent coronary occlusion was found There was old subendocardial

fibrosis of the posterior interventricular septum extending from base t apex

Case 3 C W C (D U No. B1 0 255) was 64-year-old Negro woman known to be diabetic for at least four years. She was hospitalized t Duk Hospital in 1945 for term delivery and in 1956 for nfection of her hand. In 1956 he ECG had re vealed right bundle branch block. There was no past history of documented myocardial infarction, though there had been some vague symptoms of chest pain, which suggested angina pectoris to some observers

The patient third and final admission was in July 1966 because of progressive symptoms of congestive heart failure and poor diabetic control. The patient showed initial improveme t on salt restriction and d uretics but on the third hospital day she suffered the gradual onset of left hemiparesis followed by gradual deterioration with progressive ongesti e failure The patient died quietly w thout y acute terminal vent. Her ECG d ring this hosp talization confirmed the previous finding of right bundle branch block but lso revealed vidence of an old diaphragmatic infarction

Postmortem examination of the heart revealed 98 per cent narrow ng of the right coronary artery 2 cm. f om ts origin p ogressing to 100 per cent occlusion by old theroma. The left anterior descending as 50 t 85 per cent narrowed and the left circ mflex artery was 70 to 95 per cent narrowed N f esh occlusions were noted Heavy fibrosis and scarring of the posterior ventricular w ll and septum were noted, with more recent scar nd necrosis involving the anterior ventricular wall nd the septum at the apex. A mural thrombus as noted at the apex of the left ventricle.

Case 4 B D B (D U No. G1 1 469) was a 69-year-old Caucasian woman, hospitalized because of acut substernal chest pain adiating to the left arm, associated with diaphoresis, nausea, and omit ing Her past history wa positive for angina pectoris There was no history of diabetes in the patient or in members of her family nd no history of hypertension or other cardiovascular disease.

The initial ECG revealed changes suggest ng acute diaphragmatic infarction and a subsequent ECG one day after admission revealed the development of a left bundle branch block pattern. Her course was marked by progressive ongestive heart fa lure and deterior tion despite nteman therapeutic efforts

Postmortem examination evealed recent th ombotic occlusion of the right coronary artery nd ecent myocardial inf rction nvolving the posterior wall of the left entricle and septum I addition there was rupture of the posterior left ventricular wall t the ite of infarction with t tendant hemopericardium

Case 5 A. J M (D L No. G5 6 018) was a 69-year-old Caucasian woma ith 6 year history of diabetes mellitus t year history of exertional angina pectoris preceded the onset of severe chest pain in J ne 1965 The int actal le nature of her chest pain caused her transfer t Duk H spital. An ECG from the previous hospital showed a normal conduction path y but the in tial ECG at Duke Hospital revealed left bundle [illegible] block pattern

The patient hospital course was marked [illegible] occurrence of shock and varying degree of [illegible] ventricular block, including transient or [illegible] heart block, and she died with a period of [illegible] arrest on her third hospital day

Postmortem examination of the heart [illegible] complete old occlusion of the anterior descending coronary artery 90 per cent old occlusion of the left circumflex artery and two points of near complete occlusion of the right coronary artery There was g oss evidence of fresh anterior myocardial infarction involving the septum, and both the anterior and posterior left ventricular walls Old myocardial scarring was also seen in the [illegible] w ll of the left ventricle and at the apex

Case 6 W S. (D U No. 8 3 950) [illegible] old Negro man, first seen as an outpatient [illegible] 1961 for complaints of dyspnea and [illegible] pain in the left arm The initial ECG revealed [illegible] nonspecific T wave changes, suggesting left ventricular ischemia A repeat tracing in [illegible] 1961 revealed a left bundle branch block pattern From 1961 to 1965 the patient had no history of myocardial infarction but in February 1965 [illegible] ECG suggested old anterior myocardial infarction There was no evidence of the previously noted left bundle branch block. In August, 1965, the patient underwent prostatic surgery for suspected [illegible] noma, and preoperative ECG again revealed left bundle branch block pattern. I November 1965 the patient was admitted to the medical service with congestive heart failure with [illegible] pleural effusion

His course was complicated by the occurrence of cardiac arrest from which he died. His ECG consistent w th interventricular conduction [illegible] and lateral w ll infarction.

Postmortem examination of the heart revealed only 40 t 50 pe cent narrowing of the right coronary artery with some discoloration of the anterior left ventricular wall nd the apex. An acute pulmonary embolus and ttendant infarction [illegible] found to involve the left lower lobe and [illegible]

Case 7 A. A. W (D U No. F7 4 275) [illegible] year-old Caucasian ma with history of [illegible] cardial infarction in November 1959 [illegible] to this, he experienced progressive difficulty [illegible] ongestive heart f ilure, and approximately [illegible] year fter his infarction he was told by his physician that he had complet heart block. He [illegible] to Duke Hospital in 1962 because of progressive refractory congestive heart f ilure Despite [illegible] improvement with intensive management, [illegible] course over the next t years [illegible] peated recurrences of severe heart f ilure, [illegible] eight hospitalizations. During his final hospitalization in September 1964 a brief trial [illegible] of transvenous pacemake [illegible] though some initial improvement [illegible] course was complicated by staph [illegible] cemia nd he died. His ECG th oughout [illegible] course revealed complet heart block with [illegible] t [illegible] tes bet een 30 and 40 beat [illegible]

Postmortem exam nation rev aled [illegible] of the anterior descending branch of the [illegible]

ronary artery beginning 2 cm. from its origin and extending for distance of 3 cm. The use of differentially colored injection media indicated collateral circulation from the right coronary system beyond the point of stenosis. An old infarction of anterior and lateral left ventricular wall and of interventricular septum were noted. There was an old mural thrombus attached to the apical endocardial all of the left ventricle. The trioventricular nodal artery had its origin from the right coronary artery

Case 8 J P D (V.A. No. 242 10-06) was 51 year-old Caucasian man who had his first myocardial infarction t age 38. Residual conduction disturbance of right bundle branch block type had been noted on his ECG. Recurrent tachycardia developed in 1961, the nature of which was unknown, but he apparently responded t therapy with digitalis and quinidine. I March 1965 the patient condition was initially evaluated t Womack Army Hospital for episodic syncope of recent onset, and was later transferred to the Durham V terans Administration Hospital because of varying first degree heart block with right bundle branch block pattern, but on occasions demonstrated second degree heart block as well. Evidence of an old anterior diaphragmatic infarct was present because of the history of syncopal episodes, ear the pacemaker as implanted int the left entricular all. This never functioned properly in that the patient maintained his own basic rhythm despite attempts t capture the heart with the pacemaker I September 1965 and January 1966 the patient was readmitted for evaluation and treatment of congestive heart It was decided not to replace the nonfunctioning pacemaker because no further episodes of syncope had occurred H final admission was in June, 1966 and was precipitated by the onset of acute chest pain His course as complicated by recurrent arrhythmias of varying first and second degree block and nodal tachycardia, and finally AV dissociation developed Although attempts t pacing with transvenous pacemaker ere initially successf l, the patient developed gram negative sepsis, shock, and eventually died.

Postmortem examination of the heart revealed variable, but at points, complete occlusion of both the right coronary artery and the anterior descending branch of the left coronary artery The trioventricular node artery arose from the right coronary but received ts blood supply via collaterals from the left coronary There ere no fresh occlusions. There was extensiv old anterior myocardial infarction ith thinning of the terior ventricular wall to form an aneurysm. The pacemaker electrodes ere implanted into the old area of infarction.

REFERENCES

1. Bauer G. E. Development of bundle branch block, Am. J Cardiol. 14:436, 1964
2. Bauer G. E Julian, D G nd Valentine, P A. Bundle branch block in acute myocardial infarction, Brit. Heart J 27 724 1965
3. Master A. H Dack, S., nd Jaff H. L. Bundle branch block and intraventricular block in acute coronary occlusion, Am. Heart J 16:283 1938.
4. Penton, G. B Miller H., and Levine, S. A. Some clinical features of complete heart block, Circulation 13:801 1956.
5. Johnson, C. C., and Miller P F The occurrence of arrhythmias in acute myocardial infarction, Dis. Chest 33:414 1958.
6. Julian, D G V lentine, P A., and Miller G. G Disturbances of rate, rhythm, and conduction in acute myocardial infarction, Am. J Med 37:915 1964.
7. Kurland, George S nd Pressman, D The incidence of arrhythmias in acute myocardial infarction studies with constant monitoring system, Circulation 31:834 1965.
8. Courter S. R., Moffat, J and Fowler N O Advanced trioventricular block in acut myocardial infarction, Circulation 27 1034, 1963.
9. Mintz, S. S., and Katz, L. N Recent myocardial infarction. Arch I t. Med. 80:205 1947
10. Bauer G Transient bundle branch block, Circulation 29 730, 1964
11. Comeau, W J Hamilton, J G M and White P D Paroxysmal bundle branch block associated with heart disease, Am. Heart J 15:276, 1938.
12. Graybiel A and White, P D Complete auriculo-ventricular dissociation, Am. J M Sc 192:334 1936.
13. Blondeau, M Rizzou, P and Lenègre, J Les troubles de la conduction auriculo-ventriculaire, dans l'infarctus myocardique recent. II Étude anatomique Arch. mal coeur 54 1104 1961
14. Lenègre J Les blocs auriculoventriculaires complets chroniques. Étude des causes et des lesions à propos de 37 cas Mal. cardiovas. 3:311 1962
15. Lev M and Unger P N The pathology of the conduction system in acquired heart disease. I Severe trioventricular block, Arch. Path. 60:502, 1955.
16. Lev M Widran, J and Erickson, E. E. A method for the histopathologic study of the trioventricular node, bundle, and branches, Arch. Path. 52:73 1951
17. Lenègre, J and Chevalier H Note technique préliminaire concernant l'étude histologique de la cloison d coeur Arch. mal. coeur 44:512, 1951
18. James, T N Morphology of the human trioventricular node, with remarks pertinent to its electrophysiology Am. Heart J 62 756, 1961
19. James, T N and Burch, G. E. The blood supply of the human interventricular septum Circulation 17:391 1958.
20. Spalteholz, W Die Arterien der Herzwand, Leipzig 1924 S. Hirzel.
21. Gross, L. The blood supply to the heart, New York, 1921, Pa l B Hoeber Inc.
22. James, T N Anatomy of the coronary arteries, New York, 1961 Pa l B Hoeber Inc.
23. James, T N Anatomic relationship of coronary occlusion t the blood supply of the sinus node and atrioventricular nod In the

etiology of myocardial infarction *in* The etiology of myocardial infarction Henry Ford Hospital International Symposium Boston 1963 Little Brown & Company pp 311 337

24 Estes, E H J Entman, M L Dixon, H B III and Hackel, Donald B The vascular supply of the left ventricular wall Am Heart J 71:58, 1966

25 Pickett J T and Sommer J R Thirty five mm film mounting base and plastic spray as cover glass for histologic section Arch Path 69:239 1960

26. Mahaim I Les maladies organiques du faisceau de His-Tawara les syndromes coronaires l'endocardite septale l'infarctus septal, Paris, 1931 Masson et Cie

27 Lev M The pathology of complete atrioventricular block, Prog Cardiovasc Dis 6:317 1964

28 Lenegre J : Etiology and pathology of bilateral bundle branch block in relation to complete heart block Prog Cardiovasc Dis 6:409 1964

29 Blumgart, H. L., Schlesinger M J and Davis D Studies on the relationship of the clinical manifestation of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings Am Heart J 19:1, 1940

30 Edwards, J E Pathologic spectrum of chronic coronary arterial disease, Lab Invest 5:475 1956.

31 Paulk, E. A., Jr and Hurst, J W Complete heart block in acute myocardial infarction clinical evaluation of the intracardiac bipolar catheter pacemaker Am J Cardiol 17:695 1966

Guanethidine and bethanidine in the management of hypertension

Marvin Moser, M.D.
White Plains, N. Y.

The availability of guanethidine (Ismelin) as an effective blood pressure lowering agent has simplified the management of patients with moderately severe or severe hypertension. This drug selectively interferes with sympathetic nerve transmission without interfering with parasympathetic functions.

Mode of action

The primary action of guanethidine is dependent upon (1) its ability to block the release of norepinephrine at sympathetic nerve endings without interfering with neural conduction and (2) partial depletion of norepinephrine stores in the heart and other organs. These physiologic effects prevent proper sympathetic nerve response. Myocardial depletion of norepinephrine is not so complete as noted after reserpine. Sympathetically innervated cardioaccelerator fibers are, however, blocked by guanethidine. When blood pressure falls, an increased cardiac rate often occurs. This compensatory tachycardia is blocked by guanethidine.

The norepinephrine content of the brain is not significantly altered by guanethidine since the drug is a lipid insoluble agent which does not cross the blood-brain barrier in appreciable amounts. Unlike reserpine, guanethidine does not, therefore, produce a sedative effect along with blood pressure lowering.

Physiologic effects

Acute administration of guanethidine results in a substantial reduction in cardiac output secondary to reduced venous tone, consequent peripheral venous pooling, and a fall in venous return. Only a slight reduction in renal vascular resistance occurs. Thus, the fall in arterial blood pressure that results from decreased cardiac output is usually associated with a reduction in renal plasma flow and glomerular filtration rate.

When given intravenously, guanethidine is extremely potent with a rapid onset of action. A transient rise in blood pressure may be noted, presumably due to release of norepinephrine from tissue stores (before depletion has occurred). We have not utilized guanethidine intravenously because of the possibility of this reaction. This transient pressor phase is not seen after oral administration of the drug, and some investigators who have given the drug intramuscularly in hypertensive crises have not observed a pressor response.

When administered orally in therapeutic doses, guanethidine produces a lowering of blood pressure, mainly in the standing position, without many of the side effects, such as bladder atony and gastrointestinal symp-

*Physician-in-charge, Hypertension Section, Montefiore Hospital and Medical Center, New York, N. Y., and Associate in Clinical Medicine, Albert Einstein College of Medicine, New York, N. Y.

toms, occurring with ganglion blocking agents such as mecamylamine Arteriolar and venous dilatation results from the sympathetic nerve blockade produced by guanethidine Although these effects are not as pronounced as when the drug is given intravenously some pooling of blood in splanchnic and peripheral beds does occur with a reduction in cardia utput and reduction in renal cerebral and coronary blood flow These physiologi changes are increased in the standing position and must be kept in mind when using any sympathetic block ng drug Patients with cerebrovascular cor nary artery or renal disease must be treated cauti usly as a precipitous fall in blood pressure can produce serious reactions Obviously irculatory adjustments occur after prolonged blockade with any drug and experience has not indicated serious long term effects from the above alteration in flow to vari us organs On the contrary in many cases prolonged blood pressure reduction has resulted in salutory effects n card vascular and possibly renal fun t on

Onset of action and dosage

The nset f action of guanethidine is slow A clinical response often requires three to four days after treatment is begun The drug effects disappear slowly following a single large oral dose some evidence of drug action may persist for three to seven days or longer in patients with impaired renal function and or heart failure The effect on blood pressure therefore is cumulative and may not be maximal until the drug has been given for several days. There is no set dosage of guanethidine in a patient with hypertension The dosage must be increased until the desired blood pressure lowering effect has been achieved or until reactions such as symptomatic postural hypotension preclude further therapy A dramatic blood pressure response may occur in some patients following 10 mg a day of guanethidine while others may require 250 to 300 mg daily Unlike the Rauwolfia drugs, the thiazides, or hydralazine, which have fairly well-standardized dosages, increasing the dose of guanethidine frequently increases the response. Since guanethidine is usually used only in cases of severe hypertension with organ system involvement, dosage should be increased until the desired result is obtained even if some side effects occur

Small doses of guanethidine are given on an ambulatory basis (10 mg per day as a single dose) and increased gradually by increments of 10 mg every three to five days until the desired effect is obtained (normotensive or near normotensive blood pressure levels in the upright position) Blood pressure titration should be carried out based upon standing blood pressures since the first and major effect of the drug is an orthostatic one If recumbent blood pressures are used pressure reduction may not be detected and an overdose of the drug given Since the duration of action is prolonged a once a day dosage schedule is usually effective

Guanethidine should rarely be employed as initial or sole therapy because of its potency The patient therefore should receive a diuretic agent and or a Rauwolfia drug and or hydralazine prior to the use of guanethidine Diuretic drugs, by virtue of their effect on plasma volume, increase the effectiveness of sympathetic-blocking agents. Prior use of these drugs, as well as Rauwolfia derivatives and or hydralazine makes it possible to achieve the same blood pressure lowering effect with lower doses of guanethidine and therefore fewer side effects.

Several months may be required to produce a satisfactory blood pressure level in patients with severe hypertension, despite the use of two three or even four drugs in combination Blood pressure may be extremely labile during the early weeks of therapy with occasional peaks to pretreatment levels These peaks will become less frequent and lower over a four to six week period of time. Finally normotensive levels will be noted once or twice daily with late afternoon rises in blood pressure. If the patient responds satisfactorily blood pressure will level out and control will become easier as the blood pressure thermostat (the baroreceptors?) is reset at a lower level. This type of response is, however not always noted.

In approximately 15 per cent of patients complete control of blood pressure over a

4 hour period of time is not possible despite large doses of guanethidine and one or more of the above drugs. Blood pressure levels will be extremely low in the early morning and will frequently rise significantly by late afternoon or early evening. Juggling of dosages, or the time and frequency of drug administration, will rarely be totally effective in these cases. A shorter acting adrenergic neurone-blocking agent, bethanidine, may offer some advantages in these situations.

We have treated over 250 patients with guanethidine, in combination with other antihypertensive agents, over the past 9 years with good results in over 80 per cent.

Side effects

Dizziness and weakness are the most frequently noted side effects following guanethidine. Diarrhea, bloating, gas pains, and indigestion also occur in some patients. The latter symptoms may prove troublesome and are a result of relative overactivity of the parasympathetic nervous system. Occasionally they persist and are severe enough to warrant stopping the drug.

Guanethidine does not decrease libido or prevent orgasm, but does cause a failure of normal ejaculation. Ejaculation occurs into the urinary bladder as a result of sympathetic blockade of reflex closure of the sphincter at the proximal urethra at the time of orgasm. Male patients should be advised of this possible reaction and assured that it is not harmful.

Early morning weakness and lightheadedness upon assuming an upright position is a frequent complaint in patients who have achieved normotensive or near normotensive blood pressure levels on guanethidine. This symptom tends to disappear later in the day. It is probably secondary to a redistribution of fluid during the night, as the patient remains in the recumbent position plus a sleep-induced maximal relaxation of vasomotor reflexes. When the patient rises in the morning, venous pooling occurs in the legs where tissue pressure is low and venoconstriction has been blocked by action of the drug. As fluid accumulates in the lower extremities during the day, tissue pressure increases, less blood is pooled in the legs when the patient stands, and orthostatic blood pressure changes (and weakness) are decreased. Patients should be cautioned to arise slowly. Orthostatic hypotension can be minimized in some patients by using seven to nine inch blocks under the head of the bed. This may increase the nocturnal blood pressure lowering effect of guanethidine and may also prevent redistribution of fluid away from the lower extremities while the patient sleeps. In other patients, afternoon fatigue and weakness secondary to postural hypotension may occur.

It is the physician's responsibility to explain to the patient that one or more of the above side effects may occur when guanethidine is used. Frequently, these symptoms will decrease after several weeks. For this reason the drug should not be discontinued unless reactions are fairly severe, especially if a satisfactory blood pressure response has been obtained. If blood pressure is inadvertently lowered excessively, the dosage of the drug should, of course, be reduced. A small percentage of patients will not be able to tolerate the severe weakness that may persist on continuous administration of the drug. In these individuals other drugs must be substituted.

Summary

1. Guanethidine is a potent, orally effective sympathetic blocking drug which also blocks the cardioaccelerator fibers. It has no direct effect upon parasympathetic nerve transmission.

2. The major effect of guanethidine is produced by (A) blocking the release of norepinephrine at the sympathetic nerve endings and (B) partial depletion of norepinephrine stores in the heart and periphery.

3. The clinical effects of the drug in hypertensive patients are arteriolar and venous dilatation resulting in a fall in cardiac output and blood pressure, especially in the upright position.

4. Side effects include gastrointestinal symptoms and failure of ejaculation. Orthostatic hypotension, weakness, and bradycardia are indications of excessive drug effect.

5. Guanethidine, in combination with

diuretics and Rauwolfia drugs is effective in the treatment of the moderately severe and severely hypertensive patient. The drug should not be used in patient with mild hypertension or as th sole therapy because of its potency and occasional difficulty in dosage regulation. Dosage must be adjusted carefully until a blood pressure response or side effects occur.

Bethanidine sulfate

Bethanidine sulfate (1-benzyl-2,3-dimethyl guanidine sulfate) is a relatively new compound, not yet commercially available in the United States, that inhibits the release of norepinephrine at sympathetic postganglionic neuroeffector junctions without preventing the actions of norepinephrine. Norepinephrine depletion occurs on prolonged use of the drug, but to a lesser degree than with guanethidine.

Bethanidine is absorbed from the alimentary tract and is a potent antihypertensive drug. Comparative studies with guanethidine reveal that the drugs are similar in potency and produce similar side effects with one exception. Diarrhea rarely occurs with bethanidine.

Duration of action is relatively short. Onset of action occurs within 4 to 6 hours with total duration of effect between 8 and 12 hours. This presents some advantage over guanethidine if more rapid blood pressure lowering is desired. The short duration of action may be helpful in some patients where larger doses may be given late in the day to prevent afternoon or evening blood pressure rises.

Bethanidine is administered three to four times daily starting with 10 mg. doses. Increments of 5 to 10 mg. a day are added until an effective dosage is achieved. This may vary from 50 to 500 mg. daily. The concurrent use of a diuretic reduces the amount of bethanidine necessary to lower blood pressure.

Some tolerance to bethanidine develops in a small number of patients. Side effects such as postural hypotension and weakness are occasionally more troublesome than with guanethidine.

Bethanidine may be useful in selected patients who develop persistent diarrhea or marked diurnal blood pressure fluctuations with guanethidine.

REFERENCES

1. Page, I. H., and Dustan, H. J. A. M. A. 170:1265, 1959.
2. Richardson, D. W., Wyso, E. M., Magee, J. H., and Cavell, G. C. Circulatory effects of guanethidine. Clinical, renal and cardiac responses to treatment with a novel hypertensive drug. Circulation 22:184, 1960.
3. Frohlich, E. D., and Freis, E. D. M. Ann. District of Columbia 28:119, 1959.
4. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. I. Pharmacology of [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate (Su-5864). J. Pharmacol. & Exper. Therap. 128:22, 1960.
5. Moyer, J. H., and Brest, A. N. Drug therapy of hypertension. I. Observations on the response with ganglion-blocking agents given in combination with Rauwolfia and chlorothiazide. Arch. Int. Med. 108:21, 1961.
6. Boura, A. L. A., and Green, A. F. Adrenergic neurone blockade and other acute effects caused by N-benzyl-N′,N″-dimethylguanidine and its ortho-chloro derivative. Brit. J. Pharmacol. & Chemotherapy 20:36, 1963.
7. Johnston, A. W., Prichard, B. N. C., and Rosenheim, M. L. The use of bethanidine in the treatment of hypertension. Lancet 2:659, 1964.
8. Gifford, R. W. Bethanidine sulfate—a new antihypertensive agent. J. A. M. A. 193:901, 1965.

Annotations

Effects of experimental intracranial hemorrhage on the ultrastructure of the myocardium of mice

Characteristic electrocardiographic changes are frequently associated with acute cerebral hemorrhage, suggesting an ischemic cardiomyopathy. Previous studies in this laboratory using histochemical techniques indicated the presence of myocardial lesions in some mice resulting from experimentally induced intracranial hemorrhage. Ultrastructural myocardial changes also occur in mice after simulated intracranial hemorrhage.

Twelve adult HaM/ICR mice were injected intracranially along the midsagittal line with 0.03 ml. of blood collected from littermates which had been put to death. The animals were killed on the sixth day after injection. Eight uninjected animals



Fig. 1



Fig

were sele t d f om the sam litters as controls. (h F art ere q ickly excised fter the mice wer k lled Small tissue samples were tak from ea h of the fou ardiac hambers nd immediately processed for electron m roscopic examination.

A f irly haracteristic series of ltrastructural lterations were observed in focal reas of the myo- ard um the experimental nimals (Fig 1). The m tochondria showed arious states of degeneration They were swollen with a decrease in the n mber of rista (M) Their matrices often demonstrated signific t reduction i electron density Some of the m tochondria exhibited vacuolation, whereas others had additional surrounding membranes (Fig 1) There were several multilayered structures (MS) occupying interfibrilla positions along w th the mitoch ndria (Fig 1) These truc tures were irregular in shape had matrices of re duced electron density and were bounded by 3 to 6 osmiophilic membranes. A few transversely cut cristae were noticeable within their matrices. Numerous lipid bodies (L) were freque tly associated with the altered mitochondria (Fig).

The sarcoplasmic reticulum (SR) was markedly dilated (Fig 1). This as frequently the most prominent change noticed within the affected areas of myocardium The myofibrils of some specimens demonstrated a conspicuous lack of striations. The Z bands in such fibrils were indistinct or barely identifiable (Fig 1). The actin and myosin filaments were reduced in thickness and tended to blend together giving the appearance of focal dissolution of sarcomere segments. The chromatin granules of nuclei in the damaged myofibers ere ... tributed along the nuclear membrane.

Electron microscopic changes in the ... myofibers ried n degree in different ... and these changes suggest possible ... myocardial anoxia. Simila changes in ... sarcoplasmic reticulum nd myofibrils have ... reported by other estigators under d... hypoxic conditions.

Although electrocardiographic changes ... be adequately related to ultrastructural ... produced by damage to the brain at this time, ... dence of significa t myocardial injury has ... observed in this experimental model. The ... obser ed in sarcoplasmic reticulum ... in the light of its f nction in excitation-... coupling seem significant. The neurogenic ... nisms responsible for such "sympathetic ... need elucidation.

G. E. Burch, M.D.
R. S. Sohal, Ph.D.
S. C. Sun, M.D.
H. L. Colcolough, M.D.
Department of Medicine
Tulane U ersity School of Medicine
and the Tulane ...
New Orleans, La. 7011...

REFERENCES

1 Burch, G. E., Myers, R., nd Abildskov J. A. A new lectrocardiographic pattern observed in cerebral accidents, Circulation 9:719, 1954

2. Cropp, G. J. and Manning, G. W. Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage. Circulation 22:25, 1960.
3. Burch, G. E., Sun, S. C., Colcolough, H. L., DePasquale, N. P. and Sohal, R. S. Acute myocardial lesions following intracranial hemorrhage in mice. A histological and histochemical study. Arch Path 84:517, 1967.
4. Bryant, R. E., Thomas, W. A. and O'Neal, R. M. An electron microscopic study of myocardial ischemia in the rat. Circulation Res 6:699, 1958.
5. Burdette, W. J. and Ashford, T. P. Response of myocardial fine structure to cardiac arrest and hypothermia. Ann Surg 158:513, 1963.

Atrial fibrillation and digitalis toxicity

When patients who are taking adequate and yet apparently excessive amounts of digitalis for atrial fibrillation undergo precordial electric countershock—"Cardioversion"—serious arrhythmias may be precipitated. Furthermore an unexpectedly slow heart rate during exercise in sinus rhythm may then be found. Although it is generally agreed that digitalis should be omitted for several days before the procedure is undertaken, there is some difference of opinion as to the mechanism of these phenomena. Lown and colleagues[1] showed that glycosides increase the sensitivity of the heart to electric shock, so that less energy is required to produce ventricular tachycardia or fibrillation when ouabain or acetylstrophanthidin has been given. This does not account for the appearance after shock of A-V block and sinus bradycardia. Elkins and co-workers[2] considered the hypothesis that a given level of digitalization may be tolerable during atrial fibrillation but toxic later because of the acute change to sinus rhythm. They studied the cumulative dose of acetylstrophanthidin needed to produce acute toxicity (sustained ventricular tachycardia or complete A-V dissociation with nodal tachycardia) in dogs in sinus rhythm or in atrial fibrillation. They found the toxic level to be 10 to 30 per cent greater during atrial fibrillation.

There is a further factor that has not been emphasized before. The common disturbances of rhythm due to digitalis may not be apparent simply because of the atrial fibrillation, whereas they may very well have been clear had the dominant rhythm been of sinus origin. Digitalis toxicity may be masked by atrial fibrillation. This small masking effect may be of vital importance when digitalis is given according to the formula, time-honored and recently re-emphasized,[3] to slow the heart to 70 or 90 beats per minute without pulse deficit and the rate show little rise with effort.

The common arrhythmias associated with digitalis during sinus rhythm include A-V block, ventricular extrasystoles perhaps multiform tending to bigeminy, ventricular tachycardia, and fibrillation, paroxysmal supraventricular tachycardia with varying block, and accelerated junctional rhythms. All of these are importantly modified during atrial fibrillation. First- and second-degree A-V block and atrial tachycardias will not be diagnosable. The modifications of the ventricular extrasystolic and junctional rhythms are analyzed below.

During sinus and other regular rhythms, a single ventricular extrasystole is followed, as a rule, by a compensatory pause. This long pause tends to precipitate a further extrasystole—the "rule of bigeminy."[4] The alternation of longer and shorter pauses is a potent factor in the maintenance of the bigeminy. During atrial fibrillation, on the other hand, a fully compensatory pause is not seen. There may be some attempt at a pause because of the concealed penetration of the ventricular impulse into the A-V node. The pause is prematurely terminated by the next conducted atrial impulse. A clear-cut, self-perpetuating alternation of long and short cycles would not, therefore, be established unless the factors inducing the extrasystoles were present to a much-increased extent. That is to say, digitalis induced ventricular extrasystoles are more likely to result in sustained bigeminy if the dominant rhythm is regular. A tracing consisting of strips of 12 leads may contain only one or two extrasystoles. The report may read "Atrial fibrillation with occasional ventricular extrasystoles." For a similar patient who is in sinus rhythm and has digitalis toxicity of exactly the same intensity, the report may well read "Ventricular extrasystoles, tendency to bigeminal rhythm," and the significance is immediately apparent. When the strips are short and ectopic beats few, two further factors militate against the correct pragmatic inference being drawn. The distinction of ectopy from aberrant intraventricular conduction is more difficult, and may be impossible. Secondly, the significant point that the ectopic beats are multiform may not emerge.

Glycosides enhance the automaticity of ectopic pacemaker tissue while depressing conductivity. When the activity of an A-V junctional pacemaker is enhanced so that its rate is faster than that of the sinus and in addition retrograde A-V nodal conduction is interrupted by interference or impaired by block, the A-V junctional rhythm becomes manifest and A-V dissociation results. If forward

conduction is possible entra ... pt ure beats may occur when the sinu impulse su tably timed Since the at ial act t m f brillation is raped en tricular captures are more lik l tha n sinus rhythm unless the depres on of A V nduction more intense that t sa les ther more A V block The rate of ac ler ted A V junctional pacemaker nd the de ired ont illed onducted t atrial fibrillation ften both about 70 to 90 beat per m nut An m ompl t A V funcl ation in such tr mstanc not n uncommon arrhythmia The diagnost riteria ha long been known but the diagnosis req res patie t sear h for the telltale A V j nct mal esc pe terval If the junctional beat how ter t or pref erential condu the diagnosis much easier The sig f nc of ompletl y regular entricula rhy h l ng trial fibrillation is not small le k 3 (les umed t be due t pontaneou es on t nus hythm) Com plete A V l k wit however requires more depression of luctri t or enhancement of ectopic mp l e f at in than loes the les ea l potted t ll irregula n ompl et f orm

Thu ll the m mon rrh thmia that may wa of dig talis toxi ber t les frequent or dim nished b he presence of t ial fibrillation It takes m e ff t of dig tal t produce digitalis rrh h n h the dom na t hythm is trial fibr llat ha when ther is sinu rhythm These ob serv re of reles nce three ... t (1 the ev luation of experimental esult wher h thm hange is an endpoint such ... in linical medicine when a ha ge ... bod ternal m beu n sociated with the precipitation of digitalis toxicity g pulmonary embolism pneumonia, potassium loss or precordial ountershock and (3) in the use of ... special pical rat as an endpoi t for the bioassay that is digitalization.

H David F edberg M B.(Rand) M.R.C.P (Lond)
Chief Cardiovascular Section
Veterans Adm stration Center
W ood W is
A sistant P fessor of Medic ne
M quett School of Medicine
Milwa kee W is

REFERENCES

1. Gilbert, R., Eich R. H Smith ... B ... ley J and Auchincloss J H Jr Circulation of conversion of trial fib... to sinus rhythm Circulation ...
2. Gilbert R nd Cudd ... R. P Dyn ... tory ... tion following conver ... Circulation 32:58, 1965
3. Lown B Kleiger R., nd Williams J Car... version and di italis drugs, Charged ... to electric shock in digitalized ... Circulation Res. ...:519 1965.
4. Kleiger R., nd Lown, B Cardiover ... digit lis II Clinical studies Circulation ... 1966
5. Elkins, R. C. Vasko, J S and Morrow ... Digitalis tolerance during atrial fibril... and normal ... u rhythm, Am J Card ... 20:219 1967
6. Bellet, S At ial fibrillation in the elderly patient, Geriatrics ...:239 1966
7. Ka tor J A and Yurchak, P M Recog... of dig talis intoxication in the presence of atrial fibrillation, Ann I t. Med 6... 1965
8. F iedberg C. K., and Donoso, E Arrhythmias and onduction disturbances due to digitalis I ... Cardiova Di 2 406 1960.
9. Langendorf R. Pick, A., and Winternitz, M. Mechanisms of interm ttent ventricular bigeminy I Appearance of ectopic beats dependent pon length of the ventricular cycle the rule of bigeminy Circulation 11:... 1955
10. Hwang W and Langendorf R., Atrioventricular nodal escape in the presence of atrial fibrillation, Circulation 1:930, 1950
11. Pick A. Aberra t ventricular conduction of escaped beats. Preferential and accessory pathways in the A V junction, Circulation 13 ... 1956
12. W lsh, T J Ventricular aberration of A-V nod l escape be t Comment concerning the mechanism of aberration, Am. J Cardiol 10:217 1962.
13. Kistin A. D Problems in the differentiation of ventricular arrhythmia from supraventricular arrhythmia ... th abnormal QRS Prog Cardiovas. Dis. 9 1 1966.

Left atrial 'a' waves in primary myocardial disease constrictive pericarditis and arteriosclerotic heart disease

It has been stressed that cardiac catheterization studies in patients with constrictive pericarditis may closely simulate the hemodynamic finding in primary myocardial disease. The right nd left ventricular pressure, in both conditions may show an early diastolic dip followed by an early steep rise to an elevated dia tolic plateau. However ... and his co- orkers have found that in constrictive pericard tis the end-diastolic pressure in the right ventricle is equal t or abov 1/3 of the systolic pressure while in primary myocardial disease the end-diastolic pressure in the right ventricle is appro...

bly less than 1/3 of the systolic pressure. Other workers[4] have not found this to be a discriminating test.

On auscultation the most important finding in constrictive pericarditis is the loud early third heart sound, while the presystolic gallop is conspicuously absent. Wood[5] has observed that prominent or giant a waves are never found in constrictive pericarditis. However, in primary myocardial disease the presystolic gallop is a characteristic finding caused by very prominent left atrial a waves which are transmitted to the left ventricle. We recently catheterized 14 patients with primary myocardial disease of the nonobstructive type and the recorded left atrial a waves averaged 26 mm. Hg with a range of 13 to 65 mm. Hg. These large a waves were found in patients who did not show the hemodynamic changes of restrictive primary myocardial disease. The presence of prominent or giant left atrial a waves in the left ventricular pressure pulse in primary myocardial disease and their absence in constrictive pericarditis is a helpful hemodynamic discriminating test.

The presystolic gallop is a characteristic finding in arteriosclerotic heart disease patients with ventricular aneurysm while it is uncommon in compensated arteriosclerotic heart disease patients without ventricular aneurysm. Prominent left atrial a waves are transmitted to the left ventricle in patients with ventricular aneurysms. This was verified by the examination of the left ventricular pressure pulse in 5 patients with ventricular aneurysm. (The left ventricular pressures were 90/15 [= 22], 110/5 [= 14], 90/25 [= 32], 103/20 [= 28], and 98/12 [= 17].) However, in stable arteriosclerotic heart disease patients without ventricular aneurysm, the left ventricular pressure pulse does not reveal a conspicuous transmitted left atrial a wave.

The hemodynamic differentiation of primary myocardial disease and arteriosclerotic heart disease with ventricular aneurysm cannot be made by the examination of the left ventricular pressure pulse. Appropriate fluoroscopic and angiographic studies, to rule out the presence of a ventricular aneurysm are required.

Lawrence Gould, M.D.
Chief, Cardiology Section
Veterans Administration Hospital
Bronx, N. Y.

REFERENCES

1. Ny, R. E., Lovejoy, F. W., Jr., and Yu, P. N.: Clinical and hemodynamic studies of myocardial fibrosis, Circulation 16:332, 1957.
2. Baldwin, O. J., McCord, M. C., and Blount, S. G., Jr.: Clinical and hemodynamic pattern in nonspecific myocarditis: comparison with other entities also impairing myocardial efficiency, Am. Heart J. 52:130, 1956.
3. Robin, E. D., and Burwell, C. S.: Hemodynamic aspects of diffuse myocardial fibrosis, Circulation 16:730, 1957.
4. Evans, W., and Jackson, F.: Constrictive pericarditis, Brit. Heart J. 14:53, 1952.
5. Wood, P. et al.: Chronic constrictive pericarditis, Am. J. Cardiol. 7:48, 1961.
6. Gould, L., Zahir, M., Calder, B., and Lyon, A.: Non obstructive primary myocardial disease. Hemodynamic studies in fourteen cases, Am. J. Cardiol. In press.
7. McGinn, F. X., Gould, L., and Lyon, A. F.: The phonocardiogram and apexcardiogram in patients with ventricular aneurysm, Am. J. Cardiol. 21:100, 1968.

Hazardous complications of closed chest cardiopulmonary resuscitation

Minor complications of cardiopulmonary resuscitation occur frequently; these include rib fracture, costochondral separation, ecchymoses, skin burns from defibrillation, bone marrow and fat emboli, gastric dilatation, liver laceration, and traumatic pericarditis with minimal hemopericardium. Usually, these complications are of minor consequence and rarely adversely affect the course of the patient.

Life-threatening complications of cardiopulmonary resuscitation are less frequently encountered; however, we have recently treated 4 adult patients at Grady Memorial Hospital who had severe complications of closed chest cardiopulmonary resuscitation. Tension pneumothorax occurred in 3 patients and pneumoperitoneum with severe abdominal distention in one. Each was treated with needle aspiration of the thoracic or peritoneal cavity. Further details are seen in Table I.

These patients represent a definite hazard of cardiopulmonary resuscitation which involves air escape into a closed space, either in the chest or in the abdomen. Patients 1, 2, and 3 died of the initial cardiopulmonary arrest despite attempts at resuscitation. Patient 4 survived the initial cardiopulmonary arrest and pneumoperitoneum but died of a fatal arrhythmia 48 hours later.

The cause of the pneumothorax in Patients 1, 2, and 3 is unknown; however, intelligent speculation can be made regarding Patient 1 with a thermal lung injury. It is felt that vigorous external cardiac massage may have caused a burned, necrotic area of lung to rupture and extravasate air into the pleural

Table I Details on 4 patients wi h ha_ardons complic tions of cardiopulmonary resuct_n

Pat ent N	Diag m	Complication	Clue le discovery of complication (with 3 to 5 m utes after begin g CPR*)	Cours e pical
1	Thermal l ng nj ry cardiac arrest (ech sm unknow)	Ten ion pneumothor x	Difficult ventilation with manual Ambu bag	D ed E m after beginn CPR
2	B onchial th th h nic obs t pulmo nary d se pi tor rest (ech u known	Ten ion pneumothorax	Decreased breath sound nd hyper resonance t percussion of chest	Died N nu after beginng CPR
3	B nch l h th h m de ruct pulmo- na d se espir t ry arrest pr bably re lt g from cu us plug	Ten ion pneumoth rax	Difficult entilation w th manual Ambu bag	Died 15 after beginn CPR
4	A t cardial d t d est (ent ic f ar nl ll t	Tens on pneumoperitoneum th abdom nal distention	Abdom nal di tention (sever)	Died 13 hours later

*CPR di u ec

spac l l se t nd l pulmonary blebs (on n med b these patie t sociated w th h obstructiv pulmona y em ph sema probably rendered the l ng usceptible t ruptur w th ub-sequent escape of air nder tension t the pleural space. Desp t the primary lung pathoph siology in Patient 1 t 3 igorous external cardiac massage may ha used damag nd pture of norm l lung tissue ith ubsequent tension pneumothorax.

I P tie t 4 air ma ha entered the peritoneal cavit in sever l w A ext sated f om pulmo-nary parenchyma int the medu tinum following external massage ma ha dissected w thin the esophageal all to tomach or i testine w th th air entering the peritoneal vity through the serosal urface of the ntestine or stomach An ir filled viscus (stomach or small ntestine) could hav been ruptured by blunt t auma to the upper abdomen during cardiopulmonary resuscitation. In this pa tient, the free abdominal air w under ufficient pressure as t severel compromise ventilation.

These 4 patient represent life threatening com plications of cardiopulmonary resuscitation which may be recognized by alert physicians separation air from the thorax or abdomen may be life saving

Gerald F Fletcher MD
Instructor in Medicine
Emory U versity School of Medicine
Chief Resident in Medicine
Grad Memorial Hospital
Atlanta, Ga

REFERENCES

1 Baringer J R Saltman, E. W Jones W A and Friedlich, A. L. External cardiac massage New England J Med. 265:62, 1961.
2. Himmelhock S. R., Dekker A., Gazzaniga A. B and Like A. A. Closed-chest cardiac resuscitation, New England J Med 270:118 1964.

Letters to the Editor

Prompt squatting and systolic murmurs

To the Editor:

In their annotation entitled "The influence of certain drugs and of prompt squatting on the systolic murmur in hypertrophic obstructive cardiomyopathy" (pp. 293-296 of the August, 1968 issue of this Journal), Doctors Nellen, Gotsman, and Schrire refer to the bedside diagnostic value of prompt squatting on the systolic murmur in this condition. Two opposing statements are made. Whereas in the eighth paragraph, prompt squatting was noted to abolish or soften the murmur in hypertrophic obstructive cardiomyopathy, in the eleventh paragraph the authors attempted to explain the increase in intensity of the systolic murmur in this condition.

The confusion is most likely a result of misprinting, because the systolic murmur *decreases* and not increases, in intensity upon squatting in obstructive hypertrophic cardiomyopathy not only due to sudden increase in venous return but also because of raised arterial pressure and peripheral resistance. While squatting decreases the systolic murmur in hypertrophic obstructive cardiomyopathy, it increases the systolic murmur in valvular aortic stenosis or discrete subaortic stenosis.

A corrective statement seems to be in order.

Tsung O. Cheng, M.D.
Chief, Cardiovascular Laboratory
Veterans Administration Hospital
Brooklyn, N. Y. 11209

Reply

To the Editor:

Thank you for allowing me to see Dr. Cheng's letter. Dr. Cheng is perfectly correct. The mistake must, in fact, be due to a misprint.

As we indicated in the annotation and in other papers, prompt squatting abolishes or decreases the systolic murmur in hypertrophic obstructive cardiomyopathy, whereas the systolic murmurs of pulmonary stenosis, aortic stenosis, and mitral incompetence increase in intensity.

Prompt squatting thus provides a simple and safe bedside test, helping to differentiate these conditions. We suggested the mechanism to be an increase in venous return, and an increase in systemic resistance, as Dr. Cheng rightly quotes from our article.

Maurice Nellen, M.D., F.R.C.P. (Edin.),
F.R.C.P. (Lond.), F.A.C.C.
L. Vogelpoel, M.D., M.R.C.P.
Cardiac Clinic
Groote Schuur Hospital
Cape Town, South Africa

Book reviews

MECHANISMS OF CONTRACTION [illegible] THE NORMAL AND FAILING HEART. By Eugene Braunwald, M.D., John Ross, M.D., and Edmund H. Sonnenblick, M.D. Boston, 1968, Little, Brown & Company. 205 pages. Price $9.50.

This monograph presen[illegible] [illegible] papers [illegible] appeared [illegible] the *New England Journal of Medicine*. Those [illegible] read the papers before will find th[illegible] [illegible] hand [illegible]llection and ma[illegible] [illegible] the monograph [illegible]nless he ha[illegible] [illegible]lected the pape[illegible] [illegible]. The publication is good and the ill[illegible] [illegible] are very clear.

The monograph is divided [illegible] ten main sections including d[illegible] [illegible] [illegible] [illegible]ucture of the myocardium [illegible] [illegible] length-tension curve, mech[illegible] [illegible] [illegible] [illegible]ed heart muscle, myocardial energetics, [illegible] [illegible] [illegible] and other. The monograph [illegible] [illegible] the studies and publications of the [illegible] [illegible] [illegible] marized is primarily [illegible] [illegible] [illegible] [illegible] [illegible]. The bibliography is [illegible] [illegible] [illegible] although not complete or exhaustive. The leg[illegible] of the ill[illegible] [illegible] are usuall[illegible] [illegible] [illegible] the legend but not always [illegible] [illegible]. The bibliography [illegible] listed [illegible] [illegible] [illegible] however, [illegible] [illegible] of the illustrations is [illegible] [illegible] makes it difficult for the reader t[illegible] [illegible] [illegible] [illegible] [illegible] [illegible] Fig. 6. On the other hand the [illegible] of Fig. 3 and 4 are clearly [illegible] [illegible]ted.

This is [illegible] good book for the physiologist and [illegible] [illegible] [illegible] [illegible] cardiology. The clinician [illegible] would find [illegible] thorough understanding of the content of the book to be helpful in interpreting cardiac function and heart failure.

PRINCIPLES AND PROBLEMS OF ISCHEMIC HEART DISEASE. By Tinsley Randolph Harrison, M.D., and T. Joseph Reeves, M.D. Chicago, 1968, Year Book Medical Publishers, Inc. 474 pages. Price $20.00.

This is a very good, practical book written by two physicians who have had many years of experience with the many problems related to ischemic heart disease. The book is written for the practicing physician with emphasis, therefore, on the bedside problems of cardiology. Nevertheless the book is based upon physiologic principles and not upon empiric clinical ones only. The pathophysiologic discussions are equally good and as important as the clinical ones. The discussions of therapy and the emphasis on the doctor-patient relationship are extremely important for those training in cardiology. The illustrations and text are clear. The bibliography at the end of each chapter is also well selected. The book is highly recommended to students, interns, and residents as well as those training in cardiology. The physiologists [illegible] [illegible] [illegible] book useful for students of clinical physiology and a[illegible] a source of ideas concerning the [illegible] in cardiology that need study.

[illegible] [illegible] OF PHYSIOLOGIE PATHOLOGIQUE [illegible] by Jean Lou[illegible] [illegible]arrot. [illegible] 1968, Masson & Cie. 900 pages.

This monograph on the regulation of arterial blood pressure represents the contribution of French scientists and Professor Heymans of Gent, Belgium. It is a physiologic presentation [illegible] includes discussion of the baroreceptor mechanisms, the juxtaglomerular apparatus [illegible] hypertension, antihypertension action of the kidney, [illegible] [illegible] [illegible] and hypertension, the [illegible] of the brain and spinal cord in regulation of blood pressure, the heart and hypertension, [illegible] and blood pressure, [illegible] surgery and hypertension. The presentation, all in French, [illegible] [illegible] thorough and well illustrated. The bibliography following each chapter is good. The [illegible] [illegible] [illegible] find this book to be a good and [illegible] review of the regulation of arterial blood pressure. There is nothing new presented, however. Nevertheless this is [illegible] very good, accurate, and clear review of the physiologic problems. The book is worth adding t[illegible] any personal medical library.

X-RAY DIAGNOSIS OF CONGENITAL CARDIAC DISEASE. By Larry P. Elliott, M.D., and Gerold L. Schiebler, M.D. Springfield, Ill., 1968, Charles C Thomas, Publisher. 240 pages. Price $11.50.

This is [illegible] brief discussion of x-ray diagnosis of congenital cardiac defects. Unfortunately the authors use [illegible] large portion of their limited number of pages in the presentation of phonocardiograms, electrocardiograms, and even vectorcardiograms. This [illegible] was done in an attempt to correlate the roentgenographic findings with other aspects of the lesions. As a result, the book is more [illegible] book on congenital heart disease [illegible] emphasis on the radiographic manifestations. Nevertheless the presentation is clear. The illustrations are limited almost entirely to those of older children who are less difficult to treat than newborn infants and children under one year. Cardiologists working with adults [illegible] find most of this well known to them, but beginners in adult cardiology as well as pediatric cardiologists can profit from reading the book. This book is really [illegible] brief discussion of clinical cardiology. Better books are available. However the brevity of this presentation can be [illegible] feature of value to those who do not intend t[illegible] specialize in cardiology or who are beginning to learn the specialty.

American Heart Journal

April 1969 Volume 77 Number 4

Editorial

Transplantation of the heart

J F Goodwin M.D F.R.C.P F.A C C
*C M Oakley M.D M.R C.P***
London England

The most dramatic development in cardiovascular surgery during the past year has been transplantation of the human heart. The technical aspects of transplantation had already been well worked out by Shumway and his colleagues[1] when the first operation on man was performed by Professor Barnard and his team at Cape Town on Dec 3 1967 [2] The first patient died shortly after the operation but a second transplant operation carried out soon afterward was more successful. These pioneers deserve the highest praise for their technical expertise and brilliant team work. Since then over 100 transplants have been performed throughout the world and the first scientific reports are appearing in the medical press,[4,4] so it is now high time to evaluate how human cardiac transplantation stands.

Not only does the phenomenon of rejection remain unsolved, but many ethical philosophical religious, and medicolegal issues have aroused controversial and acrimonious discussions which have not been aided by massive publicity Defining death and providing suitable donors suddenly become more difficult than ever before

Current techniques of transfer of donor heart to recipient appear to be compatible with successful initial function of the transplanted heart and it seems unlikely from reports so far that the total denervation of the heart implicit in the procedure will preclude successful transplantation Although denervation is only temporary following autotransplantation reinervation of a heart transplanted from one individual to another seems unlikely and denervation is followed by almost total loss of myocardial noradrenalin Compensation of the damaged heart as well as maximum performance of the intact heart is dependent upon the integrity of the cardiac nerves to release endogenous noradrenalin in addition to exogenous medullary catecholamines, but although experimental denervation alters the manner of the cardiac response to exercise performance is hardly impaired for practical purposes provided circulating catecholamines remain available and the heart is otherwise healthy In the absence of sympathetic stimulation the heart can only increase its output through the Frank Starling mechanism whereby an increased myocardial fiber length generates a more forceful contraction Thus mechanism allows the normal heart to more than double its output solely through an increase in stroke volume. At low work loads the denervated heart therefore acts as a force pump re

From the Royal Postgraduate Medical School, London, England.
*Professor of Clinical Cardiology Consultant Physician.
**Lecturer in Medicine (Clinical Cardiology), Consultant Physician.

sponding to an increase in venous return by an increase in stroke volume. At higher work loads the exercise stimulates release of medullary catecholamines to which the sensitized denervated heart responds by tachycardia, a further increase in the force of contraction and a further rise in cardiac output.

Early after autotransplantation temporary fluid retention and hypervolemia have been noticed and may be due to loss of afferent vagal impulses from atrial stretch receptors. This condition can easily be counteracted with diuretics.

The main [illegible] to human cardiac transplantation continues to be rejection of the donor heart. The immunological characteristics of donor and host are of the greatest importance. Tissues transplanted between identical twins are usually accepted without difficulty and experience with skin and renal transplantation suggests that immunological activity varies [illegible] organ to organ, skin and kidney are highly reactive, the liver is relatively tolerant and the heart somewhere between. Avascular structures such as cornea and heart valves do not suffer from rejection phenomena. Rejection is mediated essentially through the lymphocytes of the host which together with plasma cells infiltrate the implant.[3] Edema is followed by obliterative endarteritis and these changes, unless prevented, lead to ischemia and necrosis of the graft.

Rejection may be combated either by attempting to match tissue antigens or by suppression of the immunological defences. A solution has not been reached through either approach. Some leukocyte antigen groups have been defined,[4] but there is doubt whether identification of antigens in the leukocytes of an individual necessarily aids recognition of the antigenic structure of his other tissue cells. Van Rood and his associates[[illegible]] have initiated leukocyte typing which may be done by typing the lymphocytes against selected antigenic sera. A small skin graft from donor to recipient has been extensively practiced before renal transplantation, early rejection of the graft indicating major tissue incompatibility and more prolonged tolerance a more favorable environment.

Although tissue typing is still in its infancy, Rappaport and associates[[illegible]] have already shown an encouraging correlation between leukocyte group compatibility and successful kidney grafting. Heterotransplants may also become possible if interspecies tissue compatibility can be shown to exist. One of the two additional patients reported by Cooley and associates in the addendum to their paper received the heart of a sheep but subsequently died. No human donor was available.

Lymphocyte antisera may alleviate immunological rejection of skin grafts, and Cooley and his group, modelling their method on the procedure of Starzl and associates,[[illegible]] gave antilymphocytic globulin as well as azathioprine (Imuran) and steroids to their patients. In Barnard's case radiation therapy, azathioprine, and steroids were used. Antilymphocytic globulin is particularly promising on theoretical grounds in that it may suppress homograft rejection without adversely affecting other aspects of immunology. The isolation of antilymphocytic globulin in a pure state would greatly assist suppression of rejection phenomena.[[illegible]] There has already been considerable experience with the use of antilymphocytic globulin in combination with azathioprine and prednisolone in patients who have received renal homografts. Although many patients had severe pain, tenderness and erythema at the injection site and some had anaphylactic reactions and thrombocytopenia, the one-year survival of patients receiving renal homografts was 95 per cent and no deaths could be associated with antilymphocytic globulin treatment. It should be noted that despite this promising innovation the mainstay of treatment in these patients was still steroids and much depends on a patient's ability to tolerate high doses.

At the present time the recipient of a new heart steers a perilous course between the Scylla of rejection and the Charybdis of infection. Immunosuppressive management must be stepped up as soon as signs of rejection are noticed. These include elevation of erythrocyte sedimentation rate, increase in lactic dehydrogenase

enzyme increase in white cell count or lymphocytic ribonucleic acid incorporation development of fever reduction in effort tolerance signs of congestive heart failure fall in cardiac output, and diminution of the QRS amplitude or loss of the P wave on the ECG[4]

If cardiac transplantation is to become practicable it will be necessary to have the immunological characteristics of potential recipients documented as is already done for patients awaiting renal transplants. This would enable a potential donor to be matched rapidly with a compatible recipient. Such a plan would need to be organized on a national and possibly international basis.

The medicolegal problems involved in the selection of the donor were outlined at the beginning of this year by the Board of Medicine of the American Academy of Sciences. Rigid safeguards must be developed with respect to selection of prospective donors and an independent group of expert and experienced physicians, none of whom should be directly involved in the transplantation procedure should examine the prospective donor. They should record a unanimous opinion as to the donor's acceptability based on the evidence of crucial and irreversible bodily damage and imminent death. Such selection must inevitably involve the relatives of the donor at a time of great personal grief and the approach to them must be made with the greatest finesse

An extension of the present law to permit persons to bequeath their organs for transplantation should they prove to be suitable donors in the event of death would avoid the distasteful task of asking permission of relatives at the time of death

The donor should be preferably a young and otherwise healthy individual who had died abruptly and is free from generalized systemic disease. This qualification would limit donors to the victims of accidents involving irrevocable head injuries or to those dying from irreversible cerebrovascular accidents or disease.[22] Objective criteria of death must be obtained such as cessation of spontaneous respiration and electrical activity of the brain. Once it has been decided that the donor is beyond hope of recovery supportive measures designed to preserve the function of the heart need to be instituted since the organ to be transplanted must be viable. It should be removed from the donor within a short period of death and thereafter its viability maintained artificially. Although the heart can survive several hours of anoxia if it is immersed in saline at 2 to 4 C[1] many serious problems of preservation remain

Cardiac transplantation can only be regarded as a palliative procedure at the present time. The long term outlook of any transplant is unknown but even in the absence of overt rejection episodes a slow falloff in function of the transplanted kidney is usually seen. The candidate for cardiac transplantation must therefore be suffering from progressive irreversible heart disease with a prognosis of less than one year. Although heart disease is the commonest cause of natural death in only a fraction of the patients dying of cardiac causes will it be feasible to try to prolong their lives. In old age the heart is often only one of many declining organs and the potential transplant recipient should be reasonably healthy apart from his heart disease. The most obviously suitable individuals would appear to be those with extensively damaged myocardiums due to ischemic heart disease or cardiomyopathy as well as certain patients with rheumatic heart disease involving multiple valves and associated with severe myocardial damage. Some of the more complex forms of congenital disease, which defy present surgical techniques and which are associated with a short prognosis, could also be considered. In some of these, such as the Eisenmenger syndrome, curative cardiac surgery is prohibited only by irreversible pulmonary vascular disease, and in them transplantation of the lungs rather than of the heart would have to be carried out

While it is right that the press should be informed of the advances in transplantation and the public kept fully aware of the advances that have been made in view of the problems that have been faced and overcome and those that still remain, it is most desirable that excessive and uncon

trolled publicity should be avoided. Every unit engaged in this work should have the services of public relation officials who should issue bulletins to the press keeping them fully informed of the situation and arranging interviews between them and those concerned with the operation and care of the patients avoiding confrontation at periods of maximum stress for the operators when their responses to questions from the lay press may not be made with the discretion that they would subsequently wish.

The correct attitude to continued cardiac transplantation in man requires definition at the present time and it would now seem wise to call a halt until the problems of rejection and preservation have been more successfully met. The unhesitating way in which Dr. Barnard's lead was followed suggested that a major breakdown of the immunological barrier had been achieved. This has not been so and it is not only the public that has been carried away by the dramatic events of the past year. Prognosis in heart disease is notoriously difficult and a possible few months of uncertain existence does not necessarily justify the adoption of transplantation for the routine treatment of patients. The striking results of Cooley and his associates encourages us to believe that cardiac transplantation can sometimes offer short term palliation. Work in tissue matching and immunosuppression must be intensified until cardiac transplantation offers predictable and worthwhile prospects for patients with crippling heart disease.

REFERENCES

1. Shumway, N. E., Angell, W. W., and Woerflein, R. D.: Progress in transplantation of the heart, Transplantation 5 (Suppl.) 900, 1967.
2. Barnard, C. N.: A human cardiac transplant. An interim report of a successful operation performed in Groote Schuur Hospital, Cape Town, South Afric. M. J. 41:1271, 1967.
3. Barnard, C. N.: Human cardiac transplantation, Am. J. Cardiol. 22:584, 1968.
4. Cooley, D. A., Bloodwell, R. D., Hallman, G. L., and Nora, J. J.: Transplantation of the human heart. Report of 4 cases, J. A. M. A. 205:479, 1968.
5. Saunders, A. M., and Bieber, C.: A case of cardiac transplantation, J. A. M. A. 206:1 1968.
6. Cooper, T., Willman, V. L., Jellinek, M., and Hanlon, C. R.: Heart autotransplantation: effect on myocardial catecholamine and histamine, Science 138:40, 1962.
7. Donald, D. E.: Capacity for cardiac denervation of the heart, Circulation 38:25, 1968.
8. Donald, D. E., and Shepherd, J. T.: Response to exercise in dogs with cardiac denervation, Am. J. Physiol. 205:393, 1963.
9. Daggett, W. M., Willman, V. L., Cooper, T., and Hanlon, C. R.: Work capacity and efficiency of the autotransplanted heart, Circulation 35 (Suppl. I):96, 1967.
10. Willman, V. L., Merjavy, J. P., Pennell, R., and Hanlon, C. R.: Response of the autotransplanted heart to blood volume, Ann. Surg. 166:513, 1967.
11. Editorial: Cardiac transplantation, Brit. M. J. 3:177, 1967.
12. DeBono, A. H. B., and Warren, B. A.: Early cellular changes in homograft heart and lung tissue, Biorheology 5:01, 1968.
13. Dempster, W. J., Melrose, D. G., and Bentall, H. H.: Scientific technical and ethical considerations in cardiac transplantation, Brit. M. J. 1:177, 1968.
14. Van Rood, J. J., Van Leeuwen, A., and Bruning, J. W.: The relevance of leukocyte antigens for allogenic renal transplantation, J. Clin. Path. 20:501, 1967.
15. Van Rood, J. J., Van Leeuwen, A., Bruning, J. W., and Porter, K. A.: The importance of leukocyte antigens in renal transplantation. Abstracts of First Internat. Cong. of Transplantation Soc. Paris, 1967, p. 102.
16. Van Rood, J. J., Van Leeuwen, A., Schippers, A. M. J., Vooys, W. H., Fredericks, E., and Eernisse, J. G.: Leukocyte groups, the normal lymphocytic transfer test and homograft sensitivity. Histocompatibility testing, Ser. Haematol. 11:37, 1965.
17. Botha, M. C.: Human heart transplantation. The tissue typing tests, South African M. J. 41:1265, 1967.
18. Rapaport, F. T., Dausset, J., Hamburger, J., Hume, D. M., Kano, K., Melville-Williams, G., and Milgrom, F.: Serologic factors in human transplantations, Ann. Surg. 166:596, 1967.
19. Starzl, T. E., Marchioro, T. L., Hutchinson, D. E., Porter, K. A., Cerilli, G. J., and Brettschneider, L.: The clinical use of antilymphocyte globulin in renal homotransplantation, Transplantation 5:1100, 1967.
20. Starzl, T. E., Porter, K. A., Iwasaki, Y., Marchioro, T. L., and Kashiwagi, N., in Wolstenholme, G. E. W., and O'Connor, M., editors: Antilymphocytic serum. London, 1967, J. & A. Churchill, Ltd., p. 4.
21. James, K.: Antilymphocytic antibody. A review, Clin. & Exper. Immunol. 2:615, 1967.
22. Bosman, S. C. W.: Selection of donor for cardiac transplant, South African M. J. 41:1262, 1967.

Clinical communications

The bearing of race, sex, age, and nutritional state on the precordial electrocardiograms of young South African Bantu and Caucasian subjects

Alexander R. P. Walker, D.Sc.
B. Faith Walker
Johannesburg, South Africa

There have been several publications on electrocardiogram (ECG) tracings of American Negroes[1-4] and of South,[5-] East, and West African Negroes.[20] Abnormalities have been described which are stated to mimic pericarditis, myocardial infarction, left ventricular hypertrophy, and acute cor pulmonale. The differences between Negroes and Caucasians include persistence of the juvenile pattern in the former, greater prevalence of S-T segment elevation with or without tall T waves, and high QRS voltage. Some of the workers cited have attributed these abnormalities to race or to malnutrition. Others regard them as normal variants.[7,8,21] Still others are skeptical that valid differences do, in fact, prevail.[22,23,24] Furthermore, in contrast to other data, a recent report has indicated a greater frequency of precordial T wave inversions in Caucasian than in Negro children in response to hyperventilation.

We have been interested for some time in the sequelae of aging in interracial populations.[25,26] Controversy over the occurrence and significance of interracial differences in ECG patterns prompted our undertaking the studies to be described, more particularly on account of the possible involvement of the nutritional factor. Assuming that there are significant ECG differences in Bantu, the following questions arise: *1.* Is an ethnic factor involved? *2.* Are differences regulated by nutritional state, infections, sociocultural level, or other environmental factors? *3.* Are abnormalities, at least in young people, of prognostic significance? *4.* Since changes occur in serial studies on Caucasian[27,28] and Negro populations,[3,11,13] are the alterations of sufficient magnitude to militate against the securing of definite answers to questions *1* to *3*?

The present contribution concerns observations in the precordial tracings. Comments on those in the standard and augmented unipolar leads, abnormalities of rhythm and other features, mean amplitudes of the race-sex-age groups, and also the detailed changes observed in serial studies will be reported later.

In the assessment of tracings, even when the Minnesota Code[27,28] be employed

From the Human Biochemistry Research Unit, Council for Scientific and Industrial Research, South African Institute for Medical Research, Johannesburg, South Africa.

Supported in part by the United States Public Health Service Research Grant HE-04344 (from National Heart Institute).

Received for publication June 7, 1968.

judgments may differ from observer to observer. Hence we decided that studies on Bantu and local Caucasian populations should be undertaken under similar circumstances. This was done only by Littman, Gottschalk and Grange and Thomsen and Wasserberger in their investigations on American Negroes, and only in the case of Bantu babies in studies in Africa. We also resolved that observations should be of a prevalence character. The difficulty of ... observations to normal ... that their manner of selection ... has varied from the careful screening practiced by Blackburn and associates to the far less strict manner of selection ... the examination of Africans.

Subjects and methods

Subjects. Studies on both sexes were carried out in young children 7 to 9 years, subjects after puberty 16 to 19 years, and full-grown young adults of 20 to 29 years. Observations on Bantu were made on groups differing in region of dwelling (town ...), ... sophistication of diet, prevalence of infections, and cultural level. Observations on the Caucasian groups were confined to urban dwellers mainly in comfortable circumstances, among whom neither state of nutrition nor prevalence of infections would be likely to affect ECG patterns. Serial studies were undertaken on certain Bantu and Caucasian groups, especially the former. These are indicated by an asterisk.

The number of subjects in the different groups are given in the tables. Groups were located as follows:

Country Bantu groups

7 to 9 year: Phokeng, Mafeking
16 to 19 year: Phokeng, Imikar
20 to 29 year: Phokeng (mainly teachers), Imikazi, Thaba N'Chu (mixed volunteers)

Johannesburg Bantu groups

7 to 9 years, Meadowland
16 to 19 year: Meadowland, Orlando
20 to 29 year: Mixed group (mainly teachers)

The pupils constituted random selections; their names were consecutive entries in the age groups required on the school registers. The subjects of 20 to 29 years were volunteers; although refusal rate was 20 to 25 per cent, we consider that those examined were representative.

Johannesburg Caucasian groups

7 to 9 years: Salvation Army Home, Langlaagte Home
16 to 19 years, Mixed volunteer group
20 to 29 years: Mixed volunteer group, student group

The young were selected from those in homes because refusal rate would be lower than in state or private schools; actually there were no refusals. In the older age groups, refusals occurred in ... and 10 per cent, respectively, of those approached.

Nutritional status. The indices used for assessment are based in part on recommendations by Jelliffe.[29]

ANTHROPOMETRIC MEASUREMENTS. These included weight, height, and skinfold thickness (triceps and scapula) using a Harpenden callipers. Ponderal index was calculated from the usual formula.

BIOCHEMICAL TESTS. Serum cholesterol was estimated by a modification of Pearson's method.[31] Whereas, in initial studies, cholesterol was determined in individual serum samples, later when it became apparent that the nutritional and other factors were not of overriding importance in the ECG studies, pooled samples only were examined for the different race, sex, and age groups. Moreover, when recent laboratory studies had been carried out on groups closely similar to those involved in these studies, such laboratory data were used and further tests not undertaken.

BLOOD PRESSURE MEASUREMENTS. These were made on certain Bantu groups to supplement the ECG high voltage studies. Values were estimated with subjects in the sitting position. When measuring diastolic pressure, disappearance of sound was taken as the endpoint.

Infection status. Changes in T wave and S-T segment are known to be affected by infections.[32] These are common in Africans.[33] In the Transvaal, schistosomiasis is prevalent in certain country regions but far less so in towns; the reverse is the case with ascariasis. This differential does not appear to apply to shigellae or salmonellae.[34] As a rough index of infection we have used erythrocyte sedimentation

rate (Wintrobe method) Rates often are high in Bantu.[25]

Cultural status Cultural level is far higher in urban Bantu than in rural dwellers.

Classification of Bantu groups Lack of space prevents the giving of all data secured.

NUTRITION In respect to nutrients when intakes are measured against recommended allowances,[26] for the bulk of older Bantu children and adults the diet is probably adequate in calories and gross protein, low in animal protein and fat, high in carbohydrate and crude fiber low in calcium usually or frequently high in iron and borderline or low (with exceptions in some groups) in most of the vitamins. The position is less favorable at least in respect to calories, at 7 to 9 years. In urban areas, the pattern of nutrient intake tends to approach that consumed by Caucasians, and includes more animal protein, fat, and sugar and usually higher intakes of mineral salts and vitamins.[29] Briefly the town compared with the country groups, in general, had a lower ponderal index i.e. heavier body build. The town groups also had a higher mean serum cholesterol level. In the best Bantu school at Orlando data for 16 to 19 years for these two parameters were much the same as those in the Caucasian groups of the same age e.g. for females, ponderal indices were 13.1 and 12.9 and mean cholesterol levels, 178 and 188 mg per 100 ml., respectively

INFECTIONS At Phokeng 4 per cent had Ascaris. At Malekutu 90 per cent had *Schistosoma haematobium* 30 per cent *Schistosoma mansoni* and 5 per cent Ascaris. At Imikazi, 25 and 12 per cent had *Schistosoma haematobium* and *Schistosoma mansoni* and 6 per cent had Ascaris. At Meadowlands and Orlando, 36 and 20 per cent, respectively had Ascaris. For 16 to 19 years mean erythrocyte sedimentation rate for country and town groups was 14 and 8 for boys, and 23 and 19 per cent for girls

CULTURE. In respect to pupils 16 to 19 year old although the schools at Phokeng Imikazi and Orlando were all secondary schools, the level of culture and extramural activities was much higher at Orlando which is one of the best urban Bantu schools in the country. A similar country versus town differential applied in respect to the younger Bantu groups

Classification problems Not unexpectedly there was considerable overlap in the data obtained also some paradoxes. Thus, Bantu girls of 16 to 19 years in Johannesburg had greater intakes of animal protein and fat and had higher cholesterol levels than Imikazi girls yet the latter had heavier body build and lower ponderal index, with greater skinfold thicknesses. Again skinfold thicknesses at 16 to 19 years were found to be similar in Bantu males, and Caucasian males in South Africa, and in England[27] Yet such data are far below figures reported for U.S. Iowa males[28] of the same age. Surely the former are not all undernourished.

Perhaps the most that can be maintained for the purpose of this paper is that the Bantu groups in urban compared with rural areas generally were better nourished less active and had a higher level of culture.

Electrocardiogram procedure

ECG tracings on Bantu were obtained usually in a large specially erected tent or a school room, which accommodated 3 wooden camp beds. The machines used were 2 Sanborn Cardio-Visettes and 1 Sanborn Visette. In the country schools, where there was no power supply a Honda 300-watt generator was used. When numerous subjects were studied in one day the last person was examined using all three machines to ensure that there was complete agreement.

Subjects were examined recumbent. They usually lay for 5 minutes before recording started. Traditionally Bantu eat little breakfast, and very little lunch the main meal being taken in the evening. We therefore had little problem over the effects of meals. Nor did changes from smoking or drugs have to be taken into reckoning. The weather almost invariably was warm or hot there was no difficulty regarding shivering

The studies on the young Caucasian pupils were carried out usually during

afternoons or Saturday mornings. Observations on the students also the other older groups were undertaken at University residences, at places of work or private houses at least an hour after a meal

Electrocardiogram items and criteria The usual 12 lead ECG was undertaken The speed was 25 mm per second and standardization was 1 millivolt equals 10 mm Items determined almost wholly were those concerned in the differences reported between Negro and Caucasian subjects

T WAVE INVERSION (1) T waves if inverted were measured deflections less than 1 mm were not recorded (2) Diphasic T waves were reported where amplitudes above and below the isoelectric line exceeded 1 mm (3) Grusin Pattern I[8] was listed namely S-T depression and inverted T wave the end deflection consisting of a deeply inverted T wave with depression of J and S-T segment bowed upwards to form a wide shoulder the whole deflection was asymmetrical with a longer lateral limb which ended in a rounded hump before settling on the isoelectric line Unfortunately neither Grusin nor other local workers specified either the extent of S-T depression or how deep the T wave must be to qualify we have regarded an S-T depression of 0.5 mm and T inversion of 3 mm as essential

S-T ELEVATION Classifications of S-T elevations of 1 to 2 mm and greater than 2 mm in any precordial lead were used to permit comparisons with other published data

HIGH PEAKED T WAVES (1) Amplitude was recorded when it exceeded (a) 7 mm as used by Grusin (b) 10 mm as used by Srikantia and associates in India and (c) 12 mm as used by Epstein and colleagues[46] in their studies on Peru Army personnel High-peaked T waves are included in Minnesota Code IX 2 although the limit of amplitude is not specified (2) Grusin Pattern II was listed separately namely S-T elevation and tall T waves in the precordial leads.[8] An elevation of 1 mm and a T wave height of 7 mm. respectively were regarded as essential

HIGH VOLTAGE. We recorded (1) high amplitude R waves when R was 26 mm. or more in V_5 or V_6 (Minnesota Co[de] III 1) and (2) we also recorded the ex[...] mum R plus maximum S waves in lea[ds] V_1 to V_6 when the total reached 45 m[m] or more as suggested by McPhie.

ASSESSMENT OF ECG TRACINGS. Trac[ings] were examined at least three times [...] by two workers using a magnifying [...] which magnified 2.5 times. Grusin Pattern I i e "T inversion with S-T depress[ion]" has been illustrated by Grusin,[8] Ford, and Gottschalk and Craige. Pattern II, i e S-T elevation with tall T wave, has been illustrated by these authors, [...] Fleishman,[1,43] Seriki and Smith,[27] [and] Thomas and associates.[4]

Results The ECG data are given [in] Tables I to VII In the calculation of [...] values only data in the first of serial [stud]ies were used In investigations on A[fr...] undertaken elsewhere and cited in the tables, some age ranges are greater tha[n] 20 to 29 years, namely Keller and Johnson 20 to 39 years, Gottschalk and Craige 17 to 30 years, Greene and Ke[...] 18 to 65 years Thomas and associates,[4] 20 to 40 years Brink[10] 18 to 50 years Fleishman[1] 20 to 40 years, Srikantia and associates,[29] 21 to 60 years, and Leather[...] 18 to 50 years The foregoing must be taken into account when making comparisons. For this and for other reasons the original papers should be consulted.

Comments on electrocardiogram results

The following points must be borne in mind (1) Allowances must be made for observer differences. In general, good agreement was reached regarding preva[...]lences of T wave inversions, tall T and [...] R waves, and high R + S voltage [...] agreement was less satisfactory in assess[...]ment of diphasic T waves and S-T changes. Borderline cases understandably presented problems. (2) The numbers in certain groups are admittedly smaller than de[...]sirable. (3) The giving of prevalences of codeable items as percentages to one decimal place implies greater accuracy than is warranted

Initially for each ECG item studied, comparisons and comments were made for each of the three age groups of Bantu and

Caucasian subjects studied. Unfortunately this treatment was found to be far too lengthy. Accordingly only a brief summary will be given *concerning each item* followed by a few points not apparent from the information given in the tables.

T wave inversion. No marked interracial differences in prevalences of T wave inversion in V_1 were found (Tables I to III). In this lead prevalences scarcely altered *in serial studies. In V_2 through V_4* changes were slightly more marked. In these leads higher prevalences in Bantu than Caucasians usually prevailed although at times Bantu groups had data similar to those of Caucasians. The most conspicuous difference was the much higher proportion of diphasic T waves in V_1 through V_4 in Bantu particularly in the younger age groups. Percentages of T inversion fell with age, more so in male subjects than in female subjects. Regarding interracial differences including persistence of the "juvenile" pattern no obvious role could be assigned to region of dwelling, nutritional state, infections, or other environmental factors.

(1) At birth prevalence of T wave in

Table I. Percentages of T-wave inversions in precordial leads in subjects 7 to 9 years

Population Group	Males						Females					
	N	V_1	V_2	V_3	V_4	Diphasic	N	V_1	V_2	V_3	V_4	Diphasic
S. A. Bantu												
Phokeng A (i)	65	96.9	78.4	41.5	9.2	49.2	75	100.0	52.0	24.0	5.3	60.0
Phokeng A (ii)	57	96.5	59.6	19.3	5.3	60.3	68	100.0	73.5	33.8	7.4	50.0
Phokeng B	50	100.0	38.0	18.0	0	38.0	50	100.0	60.0	28.0	8.0	48.0
Malekutu (i)	30	100.0	24.0	10.0	2.0	42.0	50	100.0	30.0	10.0	0	30.0
Malekutu (ii)	40	100.0	60.0	32.0	12.5	24.0	44	100.0	61.3	18.2	9.2	40.9
Meadowlands	50	92.0	40.0	10.0	6.0	34.0	50	98.0	50.0	22.0	4.0	40.0
Bantu mean	215	97.2	47.4	21.3	4.6	41.4	225	99.5	48.4	21.3	4.4	46.2
S. A. Caucasians												
Salvation Army Home (i)	30	83.3	16.7	6.7	0	13.3						
Salvation Army Home (ii)	30	86.6	20.0	10.0	0	13.3						
Langlaagte Home	39	94.9	25.6	10.3	0	7.7	33	87.8	27.3	12.1	0	18.1
S. A. Caucasian mean	69	89.8	21.7	8.7	0	10.1	33	87.8	27.3	12.1	0	18.1
Africans												
Nigeria,[a] both sexes, 8 to 9 years	40m 40f	95	85	15	5							
U. S. Negroes												
Both sexes 8 to 10 years[a]	18	100	77.7	33.0	0							
Puerto Rico												
5 to 11 years[a]	20	100	100	80	5		20	100	100	65	25	
U. S. Caucasians												
Both sexes, 6 to 7 years	40	95.0	67.5	30.0	5.0							
8 to 9 year	56	71.4	37.5	10.7	1.8							
Both sexes, 8 to 10 years[a]	65	84.6	49.3	20.0	0							

Table II Percentages of T wave inversions in precordial leads in subjects 16 to 19 years

Population Group	Male						Females					
	N	V1	V2	V3	V4	Diphasic	N	V1	V2	V3	V4	Diphasic
S A Bantu												
Phokeng A	25	44 0	12.0	4.0	0	16 0	25	88 0	6.0	0	[illegible]	[illegible]
Phokeng B ( )	100	45 0	8 0	4 0	3 0	13 0	100	83.0	11.0	1 0	[illegible]	[illegible]
Phokeng B (h)	50	40.0	6 0	2 0	2.0	14.0	50	76.0	8 0	0	[illegible]	[illegible]
Imilkan ( )	60	40 0	5 0	3.3	0	30 0	60	55 0	8.3	0	[illegible]	[illegible]
Imilkani ( )	30	40 0	3.3	3.3	0	36 6	30	60 0	20.0	6 7	[illegible]	[illegible]
Imilkani (h)	23	30 4	0	0	0	23.3	30	66.6	16.6	0	[illegible]	[illegible]
Imilkani ( )	25	40 0	12 0	0	0	28.0	28	39.2	14.2	7.1	[illegible]	[illegible]
Meadowlands	50	52.0	6.0	0	0	16 0	50	68.0	6 0	0	[illegible]	[illegible]
Orlando	75	50 7	4 0	2 7	1.3	24.0	75	72.0	8 0	4 0	1.3	[illegible]
Bantu mean	310	46 3	6 6	2 9	1.3	19 7	310	72.9	8 6	1.3	0.6	[illegible]
S A Caucasian												
Johannesburg group	50	32.0	0	0	0	2.0	50	66 0	0	0	0	[illegible]
Africa												
Nigeria 14 16 yrs	12	100	41 6	8 5	0							
U S Caucasian												
Ier m-eh	32	43 6	3 1	0	0							
Ier m-eh (	214		0				237		0			
Ier m-eh (	315		1 3				298		0 7			

versions in Bantu and Caucasian babies are reported to be much the same (2) The mean amplitude of T wave inversions in 7 to 9 year-old subjects was almost twice as great in Bantu than Caucasians. (3) In the prepuberty groups data suggested that a small part of the interracial difference could be attributed to the lighter build and slower growth of Bantu compared with Caucasians. (4) T wave inversions in Leads V and V were absent in Caucasian groups and very rare in Bantu (0.3 per cent in the 7 to 9 year-old subjects) (5) Extremely few cases of isolated midcordial T wave inversion were found (none in Caucasian and 0 1 per cent in Bantu) (6) In both races, a deep breath frequently reduced T wave inversions in V_2 through V_4 but not in Lead V_1

T wave inversion with S T depression (Grusin Pattern I) T wave inversion with S-T depression Grusin Pattern I whose prevalence varied slightly in serial studies, occurred very frequently in young Bantu, more especially in males, but decreased considerably with age After puberty a slight male sex bias was apparent. The pattern was seen less frequently in young Caucasian children and not at all in older groups. Environmental factors did not seem implicated

It should be noted that the pattern was absent in the older groups of Phokeng Bantu female subjects, and in the male and female Bantu adult groups examined by Woods and Laurie[1] Quantitative conditions for classification however were not specified by other South African workers.[11]

In U S Negroes, the pattern does occur as illustrated in Fig of the paper by Gottschalk and Craige.

Elevation of S T segment Changes of S-T segment elevation (Tables IV to VI)

Table III Percentages of T-wave inversions in precordial leads in subjects 20 to 29 years

Population Group	Males No.	V	V	V	V	Diphasic	Females No.	V	V	V	V	Diphasic
S. A. Bantu												
Thaba 'N'Chu	50	34.0	0	0	0	10.0	85	61.2	4.7	1	0	15.3
Phokeng	35	28.6	8.6	2.8	0	2.8	35	65.7	5.7	0	0	2.8
Indlcari	30	23.0	6.7	0	0	6.6	30	46.6	6.7	0	0	3.3
Johannesburg	30	33.3	3.3	0	0	3.3	30	53.3	3.3	0	0	3.3
Bantu mean	145	30.7	4.1	0.7	0	6.2	180	58.3	5.0	0.6	0	8.9
S. A. Caucasians												
Johannesburg group	35	28.6	0	0	0	9	30	53.3	0	0	0	3.3
Students	100	45.0	0	0	0	5.0	100	30.0	4.0	0	0	6.0
S. A. Caucasian mean	135	40.7	0	0	0	4.5	130	35.4	3.1	0	0	5.4
Africans												
Bantu												
Brink	50	32.0	12.0	6.0	4.0		50	46.0	8.0	0	0	
Woods	50		2.0	2.0	0		50		4.0	0	0	
Fleishman	432	13.4	1.0	1.5	1.7							
Nigeria, both sexes	50m 50f	85	36	0								
U. S. Negroes												
Keller[4]	48m 37f	34.0	1.0	0	0	10.0						
Gottschalk	150	40.7	0	0	0	1.7	150	70.7	4.0	4.0	0	3.3
Greene	39m 105f	47.1	0.7	0	0	4.2						
Thomas	277	47.8	0.7	0.3	0	6.8	43		[illegible]3	4.4	0	
U. S. Caucasians												
Gottschalk[4]	150	34.0	0	0	0	7.3	150	74.0	1.5	0	0	2.0
Tecumseh	32	31.3	0	0	0							
Tecumseh ( )	433		0.5				582		0.8			
Tecumseh (B)	478		0.8				596		0.3			
Peru	126	19.0										

in serial studies occurred they were less marked with increasing age. Elevations were common and tended to be seen in male subjects more than in female subjects. There were wide ranges of prevalences in both races this is in agreement with the findings of others. Changes with age were erratic. A greater prevalence in Bantu than in Caucasians was apparent mainly in the 20- to 29-year-old group. No conclusions can be drawn from the environmental factors responsible for the diversity of data, nor from the changes observed in serial studies. Involvement of an ethnic element is problematical.

1 The maximum elevation observed 6.5 mm occurred in a Bantu male of 18 years.

In [illegible]5 of consecutive Phokeng male and female subjects exhibiting S-T elevation, exercise reduced such either to zero or to approaching zero in [illegible]1 subjects (84 per cent). In the remaining 4 subjects (16 per cent) little or no change occurred. No difference due to sex was apparent. In the few Caucasian subjects studied re

Table IV Percentages with S-T segment changes in precordial leads in subjects 7 to 9 yr

Population Group	Males N	Males Group Pattern I	Males S-T 1-2 mm‡	Males S-T > 2 mm	Females N	Females Group Pattern I	Females S-T 1-2 mm	Females S-T >2 mm
S. A. Bantu								
Phokeng V	65	33.8	10.8	0	73	1.3	12.0	11
Phokeng V.(	57	31.6	14.0	3.5	68	26.5	16.2	[illegible]
Phokeng B	50	26.0	24.0	4.0	50	28.0	26.0	[illegible]
M lek t (	50	14.0	14.0	0	50	26.0	4.0	[illegible]
M lek tu (	40	42.5	15.3	6.6	44	29.5	11.4	[illegible]
M ad nland	50	30.0	18.0	2.0	50	24.0	10.0	[illegible]
Bantu mean	15	29.1	16.2	1.4	2.5	23.1	13.3	[illegible]
S. A. Caucasian								
Salvation Army Home	30	0	10.0	3.3				
Salvation Army Home (	30	10.0	13.3	3.3				
Langlaag Home	39	25.6	17.9	0	33	9.1	18.2	[illegible]
S. A. Caucasian mean	69	14.5	14.5	1.4	33	9.1	18.2	[illegible]
Africa								
Nigeria[*] both sexes	40m							
8 to 9	40f		23.0	3.0				

[*] [illegible] includes S-T J depression [illegible] mm
‡ [illegible] and [illegible] mm relate to S-T elevation

sponse was much the same as in Bantu. Abolition or reduction of S-T elevation in young subjects by exercise has been reported by workers in the United States[?] and South Africa.[?]

3. The effect of a deep breath on S-T elevation was very slight; a fall was evident only in 10 per cent.

Tall peaked T waves. Frequencies changed in serial studies, more so in younger than older groups. At 7 to 9 years, tall T waves of 7 mm. or more were very common; there was no pronounced interracial difference in frequency. From 7 to 9 years to 16 to 19 years, prevalences rose in male subjects but fell in female subjects, and in the latter tended to be higher in Bantu than in Caucasians. Neither the ethnic factor nor the environmental factors studied appear implicated. The much higher prevalences of very tall T waves found in Bantu men in Inukazi in healthy Italians,[?] and in the Peru Army group[44] reported upon are inexplicable.

1. Despite differences in manner of selection of subjects, and even in age groups, there is a remarkably close agreement between mean amplitude of T waves in V_1 through V_6 in Bantu men, as found by Brink,[?] Fleishman,[?] and ourselves; also in Bantu female subjects as found by Brink and ourselves. Furthermore, the figures for Bantu male subjects for leads V_2 to V_4 compare favorably not only with data on our Caucasian male subjects, but on the carefully selected American Caucasian male subjects studied by Blackburn and associates.[33]

2. In regard to Bantu and American Caucasian female subjects, the closeness of the means for T wave heights is remarkable. On the other hand, the T wave height profile for V_1 to V_6, although not V_2 nor V_6, was found to be lower in South African than in U. S. Caucasian female subjects.[?] Details of mean amplitudes will be given in subsequent publications.

Tall peaked T waves with S-T elevation

Table V Percentages with S T segment changes in precordial leads in subjects 16 to 19 years

Population Group	Males				Females			
	No.	Grusin Pattern I	S–T 1 2 mm†	S–T > 2 mm	No.	Grusin Pattern I	S–T 1–2 mm	S–T > 2 mm
S A Bantu								
Phokeng A	25	4 0	32 0	0	25	4 0	4 0	0
Phokeng B (I)	100	6 0	19 0	16 0	100	5 0	13 0	1 0
Phokeng B ( )	50	8 0	24 0	20 0	50	0	14 0	4 0
Ismkazi (i)	60	5 0	26 7	20 0	60	3 3	11 6	5 7
Ismkazi (ii)	30	6 7	33 3	26 7	30	3 3	13 3	6 7
Ismkazi (iii)	23	8 7	34 8	30 4	30	3 3	23 3	13 3
Ismkazi (iv)	25	12 0	40 0	28 0	28	3 5	10 7	0
Meadowlands	50	6 0	24 0	6 0	50	2 0	10 0	0
Orlando	75	6 6	22 4	30 4	75	1 3	20 0	9 6
Bantu mean	310	5 8	23 2	17 4	310	3 2	13 2	3 7
S. A Caucasian								
Johannesburg group	50	0	14 0	12 0	50	0	12 0	2 0
Africans								
Nigeria,[38] 14 to 16 years	12		48 0	23 0				
Masai[39]	36			19 4				
U S. Caucasians								
Tecumseh (i)[37]	214		0	0	237		0	0
Tecumseh (ii)[38]	315		0	0	298		0	0

*Grusin Pattern I includes S-T J depression > mm
†S-T changes of 1 and 2+ mm relate to S T elevation

(*Grusin Pattern II*) Changes in serial studies were marked only in the young In the 7 to 9-year-old group there were similar frequencies of tall T waves with S-T elevation in Bantu and Caucasian male groups, and in the female racial groups (Tables VII to IX) Prevalences were higher in male subjects than in female subjects. In Bantu and Caucasian males, the pattern increased with age The different frequencies found in the groups of Bantu could not be correlated with the environmental factors studied

1 In a study on males in India the pattern was not observed in the 20- to 29-year-old group but at 30 to 39 years prevalences were 16 and 6 per cent n low and high income groups, respectively No difference of this type was detected between poor and better class Bantu. Mean prevalence in the total Indian study was 7 4 per cent,

2 No data on this pattern are available for American groups, Caucasian or Negro although the phenomenon occurs in the latter as illustrated by Gottschalk and Craige and Thomas and associates.

High voltage maximum R + max mum S waves amplitude High voltage i e R + S amplitude of 45 mm or more changed less in serial studies than other ECG items studied (Tables X to XII) At birth R + S as reflected by mean RV + SV₁ has been reported to be greater in Bantu than Caucasians. This difference prevails at later ages. High voltage was very common at to 9 years, more so in Bantu than in Caucasians, and in male subjects slightly more than in female subjects. With age in male subjects, prevalences fell somewhat this occurring less in Bantu than in Caucasians. On the other hand in female subjects of both races, high voltage decreased considerably between 7 to 9

Table VI Percentages with S-T segment changes in precordial leads in subjects 20 to 29 years

Population Group	Male N	Male Grusin Pattern I*	Male S-T 1-2 mm†	Male S-T > 2 mm	Female N	Female Grusin Pattern I	Female S-T 1-2 mm	Female S-T > 2 mm
S. A. Bantu								
Thaba N'Chu	50	8.0	22.0	18.0	85	10.6	11.8	[illegible]
Phokeng	35	14.3	34.3	8.6	35	0	[illegible]	[illegible]
Ischkari	30	6.7	23.3	23.3	30	3.3	[illegible]	[illegible]
Johannesburg	30	13.3	36.7	23.3	30	6.7	16.7	[illegible]
Bantu mean	145	10.3	27.5	17.9	180	6.2	11.0	[illegible]
S. A. Caucasian								
Johannesburg group	35	0	17.1	5.7	30	0	13.3	[illegible]
Students	100	0	4.0	15.0	100	0	5.0	[illegible]
S. A. Caucasian, mean	135	0	22.2	12.5	130	0	6.9	[illegible]
Africans								
S. A. Bantu mineworkers	432			5.7				
S. A. nurses								
Grusin					50	14.0		
Woods	50	0			50	0		
Nigerians	50		92.0	35.0				
East Africa	61		44.0					
Masai	95			15.8				
U. S. Negroes								
Gottschalk	150		21.3	13.3	150		21.7	[illegible]
Thomas	277			27.0	43			[illegible]
U. S. Caucasian								
Gottschalk	150		10.0	0.7	150		10.0	[illegible]
Tecumseh ( )	433		0	0	582		0	[illegible]
Tecumseh (u)	478		0	0	596		0	[illegible]
British								
Leatham	100		55.0	8.0				
Peru	132			0.8				

*Grusin Pattern I includes S-T J depression > 0.5 mm.
†S-T changes of 1-2 and 2+ mm relate to S-T elevation.

years and 16 to 19 years thereafter It did not change with age in comparison with male subjects. Evidence suggests that the higher R + S amplitude in Bantu is primarily of ethnic origin Yet the divergent information reported in Caucasian population groups[48] as well as changes noted in serial studies, indicate that environmental factors are in operation although none of those studied by us appear to be incriminated. Differences with respect to tall R waves followed the same trend

1 Highest percentages were found in 7 to 9 year-old Bantu in Phokeng In this study the figures were 94.7 and 91.2 per cent in boys and girls, respectively more over 58.0 and 35.3 per cent had amplitudes of 60 mm. or more. Highest individual voltages in the sexes were 79 and 94 mm High voltages also were common in young Caucasian subjects, mean proportions being 37.7 and 36.3 per cent, for boys and girls but only 8.1 and 3.1 per cent had values of more than 60 mm

Table VII Percentages with tall T waves also of such waves with S-T elevation in precordial leads in subjects 7 to 9 yea s

Population Group	Males					Females				
	No.	7+ mm	10+ mm	12+ mm	Grusin Pattern II	N	7+ mm	10+ mm	12+ mm	Grusin Pattern II
S A Bantu										
Phokeng A (i)	65	3 1	1 5	0	0	75	18 7	4 0	0	6 7
Phokeng A (ii)	57	47 4	12 3	1 8	14 0	68	23 5	4 4	0	10 3
Phokeng B	50	46 0	16 0	4 0	18 0	50	28 0	8 0	0	8 0
Malekutu (i)	50	38 0	0	0	10 0	50	10 0	4 0	0	0
Malekutu ( )	40	32 5	0	0	20 0	44	15 9	2 3	0	2 3
Meadowlands	50	34 0	6 0	0	14 0	50	24 0	2 0	0	4 0
Bantu mean	218	28 4	5 5	0 9	9 8	225	20 0	4 2	0	4 9
S A Caucasians										
Salv tion Army Home ( )	30	36 7	20 0	3 3	10 0					
Salvation Army Home (ii)	30	33 3	16 7	3 3	6 7					
Langlaagte House	39	35 9	10 2	0	7 7	33	18 1	3 0	0	3 0
S. A Caucasian mean	69	36 2	14 5	1 4	8 7	33	18 1	3 0	0	3 0

Tabl VIII Percentages with tall T waves also of such waves with S-T elevation in precordial leads in subjects 16 to 19 years

Population Group	Males					Females				
	No.	7+ mm	10+ mm	1 + mm	Grusin Pattern II	N	7+ mm	10+ mm	12+ mm.	Grusin Pattern II
S. A Bantu										
Phokeng A	25	24 0	4 0	0	12 0	25	0	0	0	0
Phokeng B ( )	100	38 0	6 0	2 0	24 0	100	8 0	0	0	0
Phokeng B (ii)	50	46 0	16 0	4 0	18 0	50	6 0	0	0	2 0
Isrikari (i)	60	64 0	26 0	15 0	33 3	60	6 0	0	0	0
Isrikari (ii)	30	66 6	36 7	23 3	46 7	30	10 0	0	0	0
Isrikari (iii)	23	43 5	4 3	4 3	34 7	30	6 7	0	0	3 3
Isrikari (iv)	25	64 0	36 0	16 0	44 0	25	4 0	0	0	4 0
Meadowlands	50	22 0	12 0	0	16 0	50	10 0	0	0	8 0
Orlando	75	36 0	6 6	1 3	20 0	75	8 0	0	0	4 0
Bantu mean	310	38 ▮	11 0	3 9	22 6	310	7 3	0	0	3 2
S. A Caucasian										
Johannesburg group	50	44 0	12 0	0	12 0	50	4 0	0	0	2 0
U. S. Caucasian										
Tecumseh (i)[27]	314			4 2		337			0	
Tecumseh (ii)[27]	315			1 0		398			0	

Table IX. Percentages with tall T waves, also of such waves with S-T elevation in precordial leads in subjects 20 to 29 years

Population Group	Males N	Males 7+ mm	Males 10+ mm	Males 12+ mm	Males Gross Pattern II	Females N	Females 7+ mm	Females 10+ mm	Females 12+ mm	Females Gross Pattern II
S. A. Bantu										
Thaba 'N Chu	50	48 0	14 0	4 0	12 0	85	15 3	4 7	0	41
Phokeng	35	51 4	17 1	2 8	26 4	35	8 6	0	0	23
Inalkaz	30	63 3	26 6	20 0	33 3	30	10 0	3 3	0	8
Johannesburg group	30	40 0	16 7	5 7	20 0	30	6 7	0	0	33
Bantu mean	145	46 9	17 9	7 5	20 2	180	11 6	2 8	0	31
S. A. Caucasian										
Johannesburg group	35	51 4	14 3	5 7	17 1	30	0	0	0	8
Student	100	45 0	10 0	1 0	14 0	100	6 0	0	0	10
S. A. Caucasian mean	135	46 7	11 1	2 3	14 8	135	4 4	0	0	41
Africans										
Johannesburg	432				5 6					
Johannesburg						50				48
Pietermaritzburg	50				4 0	50				8
Durban	26				19					
Nigeria[28]	50				34 0	50				8
East African Bantu	25		5 0							
Nilot	36		2 0							
U. S. Caucasian										
Tecumseh ( )[30]	433			4 2		582			0	
Tecumseh ( )[30]	478			0 8		596			0 3	
P	132			46						
Indian[32]	941		4 3		7 4					

2 In 7 to 9-year-old children the lighter compared with heavier moiety in both races and sexes had a slightly greater mean voltage the difference being 1 to 3 mm The difference was somewhat less marked in Caucasians than in Bantu

3 Within the different Bantu female groups body build did not seem of importance Inalkazi girls with heavier body build and thicker breast tissue had higher voltages than did Meadowlands girls.

4 Using the criterion of $RV_5 + SV_1$ exceeding 35 mm in Brink's[19] series of 50 Pretoria Bantu male and female subjects 18 to 50 years old the criterion was met in 48.0 and 16 0 per cent, respectively The corresponding figures for our Johannesburg Bantu male and female groups were 44 0 and 5 3 respectively In Ea[st] Africa the proportions for Bantu a[nd] Nilotic males were 25 and 37 per cen[t] Figures for our Caucasian groups we[re] much lower 10 3 and 0 per cent for m[ale] and female subjects respectively In I[n]dia Srikantia and colleagues[32] using th[e] criterion mentioned[44] and for the sa[me] age group of men (20-29 years) reporte[d] the proportions 12 and 21 per cent, f[or] lower and higher income groups, respec[]tively

5 In babies $RV_1 + SV_1$ is reported t[o] be much greater in Bantu than in Cau[]casians[1] In the 20- to 29-year-old group despite the well known sex difference i[n] mean wave amplitudes, the higher value in Bantu was such that the sum in Bantu

Table V. Percentages with high voltage in precordial leads in subjects 7 to 9 years

Population Group	Males			Females		
	N subjects	Max. R + S > 45 mm.	Tall R > 26 mm.	N subjects	Max. R + S > 45 mm.	Tall R > 26 mm.
S. A. Bantu						
Phokeng A (I)	65	49 2	24 6	75	49 3	20 0
Phokeng A (II)	57	94 7	35 1	68	91 2	27 9
Phokeng B	50	94 0	32 0	50	40 0	22 0
Malekutu (I)	50	80 0	4 0	50	60 0	6 0
Malekutu (II)	40	80 0	5 0	44	59 1	9 1
Meadowlands	50	86 0	26 0	50	58 0	14 0
Bantu mean	215	75 3	21 9	225	51 5	16 0
S. A. Caucasians						
Salvation Army Home (I)	30	36 7	12 5			
Salvation Army Home (II)	30	33 3	6 7			
Langlaagte Home	39	38 5	2 5	33	36 3	0
S. A. Caucasian mean	69	37 7	6 8	33	36 3	0

women was closely similar to the total in Caucasian men.

6 A further point of interest is that while the reported value for RV + SV in American men 33.3 mm. is much lower than our figure for Bantu men 41 5 mm. the latter figure is virtually the same as that given for healthy Italians 41 8 mm [8] Another example of interracial difference has been reported by Epstein and associates[10] who found that R + S was a third or so greater in Peru compared with Tecumseh male subjects.

7 Kilty and Lepeschkin [7] studying young American men reported that maximum R + maximum S wave voltage decreases with increase in body build. This phenomenon was apparent in Bantu boys 7 to 9 years of age, but less so in older groups of Bantu and scarcely at all in all Caucasian male groups. The heavier half of our Caucasian male students with a mean ponderal index of 12.6 had a mean voltage of 3..0 mm. both these figures are identical to those given by the above workers.[7] However the lighter half of our students with a ponderal index of 13 4 had a voltage only very slightly higher namely 33 0 mm

8. Blood pressure levels were studied mainly in Bantu subjects of 16 to 19 years. No correlation with voltage was apparent in individuals. Mean values were found to be unchanged in serial studies. In the Insikazi study the quartiles of male subjects having highest and lowest voltages had the same mean pressures namely diastolic 62.4 ± 4.8, and 63 2 ± 5 1 mm. Hg and systolic, 115.3 ± 8 6 and 114 7 ± 9 2 mm. Hg respectively Mean blood pressures of postpuberty rural male and female subjects did not differ markedly nor were differences apparent in urban male and female subjects although values in urban areas were slightly higher ($P < 0.5$) than those in rural areas, the difference becoming more prominent in older subjects This lack of relationship between high voltage and blood pressure in Bantu subjects has been pointed out by other workers in Africa. [11, 5-14]

Comments on additional studies undertaken

SEVERE MALNUTRITION IN INFANCY AND THEREAFTER. Bantu and "Coloured" (Eurafrican) young children suffering from severe malnutrition have been reported to show low QRS voltage, flat T waves and

Table XI Percentages with high voltage in precordial leads in subjects 16 to 19 years

Population Group	Males			Females		
	N subjects	Max R+S > 45 mm	Tall R > 26 mm	N subjects	Max. R+S > 45 mm.	Tall > 26 mm
S A Bantu						
Phokeng A	25	44 0	16 0	25	0	[illegible]
Phokeng B ( )	100	77 0	14 0	100	3 0	[illegible]
Phokeng B ( )	50	70 0	10 0	50	6 0	[illegible]
Insikazi ( )	60	81 7	11 7	60	5 0	[illegible]
Insikazi ( )	30	86 7	16 7	30	13 3	[illegible]
Insikazi (iii)	23	78 3	8 6	30	6 7	[illegible]
Insikazi (iv)	25	88 0	20 0	28	10 7	[illegible]
Meadowland	50	78 0	6 0	50	10 0	[illegible]
Orlando	75	78 6	2 6	75	8 0	[illegible]
Bantu mean	310	75 8	9 8	310	5 5	[illegible]
S A Caucasian						
Johannesburg group	50	.8 0	10 0	50	0	[illegible]
U S Caucasian						
Tecumseh ( )	14		17 8	37		1 1
Tecumseh ( )	315		5 7	293		[illegible]

sharply inverted T waves.[43] We have made tracings of 15 boys and 15 girls aged 11 to 18 years admitted to the hospital when young for severe kwashiorkor While the proportions of T wave inversions also high QRS voltage were much the same as in subjects in the general population there was a lower proportion of tall T waves, and a greater proportion of sharply inverted T waves. More subjects must be examined to arrive at the true position However in the 7 to 9-year-old group of subjects we found no differences in ECG patterns between those claimed by mothers to have been consistently well and those known or stated to have had prolonged episodes of malnutrition or other sickness in their earlier years.

VERY HIGH PREVALENCE OF INFECTIONS At Malekutu Bantu School 90 and 30 per cent of pupils had *Schistosoma hematobium* and *Schistosoma mansoni* infections respectively and about a fifth had hepatomegaly The ECG pattern in 7 to 9 year-old groups did not differ markedly from that of a far less parasitized urban group of the same age

EXERCISE In normal subjects on exercise the amplitudes of QRS and T waves may be increased[53] furthermore S-T elevation often becomes isoelectric.[8,53] At different centers Bantu pupils jumped to raise heart rates to roughly 120 to 130 beats per minute for about 3 minutes Tracings were made before and approximately 1 minute after cessation of exercise. Prevalences of tall T waves, also QRS amplitude, were found to increase moreover In the subjects with S-T elevation, as already mentioned the majority became normal with exercise. The responses to exercise in the Bantu and Caucasian subjects studied were similar Regarding excessive habitual activity at a Bantu school in an isolated mountainous region in Eastern Transvaal the ECGs of 30 boys and 30 girls aged 7 to 10 years, who habitually walked a total of 8 to 12 miles daily to and from school, were compared with those of similar groups traversing only 2 to 5 miles. No differences in ECG items were apparent.

Briefly from previous as well as the above considerations, it would appear that

Table VII Percentages with high voltage in precordial leads in subjects 20 to 29 years

Population Group	Males			Females		
	No. subjects	Max. R+S > 45 mm	Tall R > 26 mm	No. subjects	Max. R+S > 45 mm.	Tall R > 26 mm.
S. A. Bantu						
Thaba N'Chu	50	22.0	10.0	85	2.4	0
Phokeng	35	68.6	20.0	35	5.7	0
Iasikari	30	50.0	10.0	30	13.3	0
Johannesburg	30	46.7	6.7	30	6.7	0
Bantu mean	145	44.2	11.7	180	5.6	0
S. A. Caucasians						
Johannesburg group	35	17.1	2.8	30	0	0
Students	100	8.0	2.0	100	0	0
S. A. Caucasian mean	135	10.4	2.2	130	0	0
U. S. Caucasians						
Tecumseh ( )[17]	453		7.1	582		0.2
Tecumseh ( )[18]	478		3.9	596		0
Peru[19]	132		1.7			

neither past nor present state of nutrition prevalence of infections, nor the other factors studied and discussed are primarily responsible for differences in the ECG pattern of Bantu and Caucasians.

Discussion

Are changes observed in serial studies of sufficient magnitude to prejudice interracial comparisons? At Tecumseh in the male groups 16 to 19 and 20 to 29 years, tall T waves, and tall R waves were much less common in the second compared with the first study.[17,18] In another type of serial study on pregnant women, S-T depression (0.5 to 0.9 mm.) was found in 8 per cent of subjects yet later in pregnancy those previously positive were positive no longer.

But apart from changes observed in serial studies, recognition must be given to the divergent character of the results obtained on groups of the same race and age range. Thus, in another study on pregnant women[36] no less than 42 per cent exhibited S-T depression in a control of nonpregnant series, the figure was 6 per cent. In the Tecumseh studies[17,18] S-T depression was absent in nonpregnant women of the same age. The wide variations in frequency of S-T elevation in groups of Caucasian subjects are apparent in Table VI. Concerning Africans Powell[12] reported S-T elevation with tall T waves in 19 per cent of young male subjects. Woods and Laurie,[13] in a similar series, reported 4 per cent. Further Turner from a study of Kikuyu Africans, reported low voltage to be common in contradiction to all other investigations on Africans which have emphasized the great frequency of high voltage. Note must be taken therefore, not only of the major changes that *can* occur in serial studies, but also of the considerable divergencies in data on certain ECG items reported for similar populations groups. The changes in serial studies seen occasionally in our own subjects particularly Bantu are thought to be real, and not to be explained away as due to artifacts or to observer errors.

Despite the drawbacks indicated it is not believed that they are sufficient to preclude comparison and discussion of

findings in respect to the bearing of race and environmental factors.

Attempts will now be made to answer the other three questions mentioned at the beginning of this paper

To what extent is an ethnic factor involved? Interracial differences in respect to a biological or other component at birth do not necessarily connote the operation of an ethnic factor, e.g., the lower birth weight in the underprivileged. Nevertheless the reactivity of different racial groups may well differ in response to the same stimulus from environmental factors. At the same time even where an ethnic factor be invoked and possibly incriminated environmental factors undoubtedly still have a regulating influence. In discussion of the role of the ethnic element in the different items studied the following points appear relevant

1 In some Negro groups,[4] T wave inversion in V_1 through V_4 is as uncommon as in Caucasian groups. While this obtained only with certain of our Bantu groups (although by and large, prevalence of this item was more common in these people than Caucasians) it does suggest that the ethnic factor is not predominantly involved

2 Diphasic T waves are far commoner in Bantu than in Caucasians in the younger age groups, although less so in adults. Such waves are also common in Puerto Rican children.[43] No explanation is suggested, the operation of an ethnic influence at least in the young seems not unlikely

3 Grusin Pattern I (T inversion with S-T depression etc.) is very common in Bantu of 7 to 9 years although much less so in older subjects. It is less common in 7 to 9 year-old Caucasians and is virtually absent in older subjects. Again no explanation is hazarded although the invoking of an ethnic influence appears plausible.

4 In respect to S-T elevation with or without tall T waves the greater prevalence in Bantu was apparent mainly at 20 to 29 years. Although characteristically prevalences were higher in these people certain groups of both sexes on occasion had frequencies similar to those of certain Caucasian groups.

5 The greater R + S amplitude found in Bantu at birth[14] continues through life. We found tall R and deep S waves [...] be approximately equally common in the upper and lower quartiles of ponderal index of postpuberty Bantu groups, thereby indicating that neither nutrition, nor the other factors studied, are markedly influential. It would thus seem that the ethnic item of almost certain ethnic origin is the high R + S amplitude in the Bantu. Yet, as previously indicated, the high value for $RV_2 + SV_5$ in Bantu male subjects, 41.5 mm, is matched by an equally high value in "healthy" Italian subjects, namely, 41.8 mm; the corresponding U. S. figure is 33.3 mm.[40]

6. While this paper deals primarily with differences in ECG items between African Negroes and Caucasians, differences have also been noted in Mexicans,[22] U. S. Apache Indians,[7] Peruvians,[46] and Indians in India.[11] Moreover, our preliminary studies have demonstrated the occurrence of such differences in South African Indian and Coloured (Eurafrican) populations. Thus the problem of ECG differences does not concern only Africans.

Although it is tempting to apportion a measure of responsibility to the ethnic factor, particularly in relation to the ge[...] of high voltage, evidence is inadequate [...] reach a firm conclusion

To what extent are differences regul[...] by nutritional state, infections, social-cu[...] level, or other environmental factors? In t[...] various groups examined and in respect [...] the parameters studied, our efforts ha[...] failed to identify the factors responsible [...] the ECG differences.

The role of fear in causing or promot[...] inverted T waves and S-T changes must [...] considered. Locally, Fleishman[13,14] su[...]ports a neurogenic explanation of abnorm[...]ities seen in Bantu. However, Bantu c[...]dren quickly get accustomed to weste[...] medical tests. In subjects exhibiting co[...] able items, we found that virtually [...] changes took place in repeat studies und[...] taken on the same day. Furthermore [...] in studies carried out on the same day [...] young Bantu children we found E[...] tracings to be almost identical, whet[...] subjects lay tranquilly in the staff ro[...] and were examined unhurriedly, or whet[...]

ents were carried out expeditiously under trees in the school playground with ball games in progress. This detached attitude has also been found with older Bantu. Regarding Caucasian children again we doubt whether fear has a significant bearing at least in a mass study. On the other hand our Caucasian female students certainly were tense, more so than the male students. But Bantu subjects have insufficient understanding to be anxious over the results of ECG tests accordingly we consider that fear has no serious bearing on their ECG tracings.

To what extent are the ECG abnormalities at least in young Bantu of prognostic significance? While our studies have provided no positive contribution to this problem the following points appear relevant.

1 Coronary heart disease is rare among Bantu, even in the sophisticated moiety.[33,34] At Baragwanath Hospital (2 500 beds) Johannesburg which serves about two thirds of a million of urban Bantu (about 20,000 being over 60 years, and 90 000 over 45 years) there are still only 2 to 3 deaths from the disease annually. In a Caucasian population of this age structure 700 or more new coronary heart disease events would be expected each year. The disease however certainly has a high prevalence in U S Negroes.[33,34] It is thus most unlikely that the ECG abnormalities in Bantu, most of which are seen in U S. Negroes have a bearing on the future development of coronary heart disease.

2. In South Africa idiopathic cardiomyopathy may account for up to a third of hospital admissions for heart disease in adult Bantu.[27,4] Fleishman [14] from his observations, considers that none of the ECG items under review are implicated in the disease which in any case is reported to be rare in U S Negroes.[34]

3 South African workers[11,13] have been unable to associate any of the ECG abnormalities described in Bantu with pathology of the heart or other organs or tissues.

4 Regarding prognosis in respect to other heart diseases, reports have suggested that congenital heart disease rheumatic heart disease hypertensive heart disease and cor pulmonale have somewhat similar prevalences in Bantu and Caucasian populations.[17,3]

Present evidence therefore does not indicate that the ECG items under discussion have adverse prognostic significance.

Summary

Abnormalities have been reported in the ECG s of Negroes, American and African in comparison with Caucasians. Items believed to be more prevalent in Negroes are T wave inversion T wave inversion with S-T depression S-T elevation with or without tall T waves, and high R + S amplitude. The responsibility borne by the ethnic factor malnutrition or other environmental factors is controversial as is even the validity of the differences. In an attempt to elucidate the situation ECG studies have been carried out on young South African Bantu and Caucasians of both sexes, 7 9 16-19 and 20-29 years of age. The Bantu studied included groups differing in region of dwelling (town and country) nutritional state infections, habitual activity and cultural level. Caucasian subjects were drawn mainly from middle class contexts. Some serial studies were undertaken. The main findings are as follows.

1 In agreement with other workers observations, wide ranges of prevalences of ECG items were found in the Bantu and Caucasian groups examined.

2 Marked changes, particularly in Bantu were noted occasionally in serial studies these varied from item to item. However neither the wide ranges mentioned nor the serial study changes, are sufficient to preclude comparisons of findings in respect to race sex, and age.

3 The most conspicuous differences found between Bantu and Caucasians were the much higher prevalences in the Bantu of inverted T waves with S-T depression (Grusin Pattern I) in the young diphasic T waves also in the young and high voltage at all ages studied as reflected by maximum R + S amplitude. None of these differences between Bantu and Caucasians or even between the various groups of Bantu of the same sex and age examined are explicable on the basis of differences in anthropometry ponderal index, nutritional

state, infections, activity or cultural level. While it is tempting to attribute these ECG differences between Bantu and Caucasians (particularly high voltage) to an ethnic factor, evidence is inadequate to reach a firm conclusion.

4. Regarding sex, a sex difference, slight or conspicuous, was apparent at 7 to 9 years in both races for all ECG items studied. In some items, e.g., T wave inversion with S-T depression in the Bantu, the differential decreased with age. In others, e.g., tall T waves with or without S-T elevation, also with high voltage, the differences became more pronounced.

5. In respect to age, in some items in both races, e.g., T wave inversion, diphasic T waves, and high voltage, prevalences decreased with age. In others, e.g., tall T waves in male subjects, prevalences rose.

6. There appears to be no evidence that ECG differences in Bantu have prognostic significance.

While Bantu and U. S. Negroes differ from Caucasians in certain ECG items, such differences are not peculiar to Negroes of African origin; like differences are seen in other non-Caucasian populations.

We are grateful for the assistance given by ... B.S., Barbara Richardson, B.S., Hamish Hart, B.S., and ... Garner. We wish to acknowledge the excellent cooperation given by the principals and staff of the schools and homes.

REFERENCES

1. Ashman, R.: An electrocardiographic study of Caucasians and Negroes, Tri-State M. J. 13: 2686, 1941.
2. Littman, D.: Persistence of the juvenile pattern in precordial leads of healthy adult Negroes, with a report of an electrocardiographic survey on 300 Negro and 200 White subjects, Am. Heart J. 32:370, 1946.
3. Littman, D.: Abnormal electrocardiograms in the absence of demonstrable heart disease, Am. J. Med. 5:337, 1948.
4. Keller, D. H., and Johnson, J. B.: The T wave of the unipolar precordial electrocardiogram in normal adult Negro subjects, Am. Heart J. 44:494, 1952.
5. Wasserburger, R. H.: Observations on the juvenile pattern of adult Negro males, Am. J. Med. 18:428, 1955.
6. Gottschalk, C. W., and Craige, E.: A comparison of the precordial S-T and T waves in the electrocardiogram of 600 healthy young Negro and White adults, South. Med. J. 49:453, 1956.
7. Greene, C. R., and Kelly, J. J., Jr.: Electrocardiogram of the healthy adult Negro, Circulation 20:906, 1959.
8. Thomas, J., Harris, E., and Lassiter, G.: Observations on the T wave and S-T segment changes in the precordial electrocardiogram of 320 young Negro adults, Am. J. Cardiol. 5:468, 1960.
9. Brink, A. J.: An investigation of factors influencing repolarization in the human heart, S. Af. J. Clin. Sc. 2:288, 1951.
10. Brink, A. J.: The normal electrocardiogram in the adult South African Bantu, S. Af. J. Lab. & Clin. Med. ...97, 1956.
11. Grusin, H.: Peculiarities of the African's electrocardiogram and the changes observed in serial studies, Circulation 9:860, 1954.
12. Powell, S. J.: Unexplained electrocardiograms in the African, Brit. Heart J. 21:263, 19...
13. Woods, J. D., and Laurie, W.: The electrocardiogram of the South African Bantu, Circulation 19:...31, 1959.
14. Fleishman, S. J.: Observations of the electrocardiogram of the apparently healthy African, M.D. Thesis, 1962, University of the Witwatersrand, Johannesburg, South Africa.
15. Fleishman, S. J.: The normal electrocardiogram in the African, S. Afr. M. J. 39:17, 19...
16. Sutin, G. J., and Schrire, V.: Inter-racial ... of the electrocardiogram in first ... Am. Heart J. 67:749, 1964.
17. Turner, P. P.: The electrocardiogram of the normal young adult Kikuyu male, East Afr. M. J. 36:555, 1959.
18. Somers, K., and Rankin, A. M.: The electrocardiogram in healthy East African (Baganda and Nilotic) men, Brit. Heart J. 24:542, 1...
19. Mann, G. V., Shaffer, R. D., Anderson, R., and Sandstead, H. H.: Cardiovascular disease in the Masai, J. Atheroscl. Res. 4:289, 1...
20. Seriki, O., and Smith, A. J.: The electrocardiogram of young Nigerians, Am. Heart J. 72:..., 1966.
21. Goldman, M. J.: RS-T segment elevation in mid- and left-precordial leads as a normal variant, Am. Heart J. 46:817, 1953.
22. Blackman, N. S., and Kuskin, L.: Inverted T waves in the precordial electrocardiogram of normal adolescents, Am. Heart J. 67:304, ...
23. Simonson, E.: Differentiation between normal and abnormal in electrocardiography, St. Louis, 1961, The C. V. Mosby Company.
24. Thomsen, J. H., and Wasserburger, R. H.: The effect of hyperventilation on precordial T waves of children and adolescents, Circulation 36:700, 1967.
25. Walker, A. R. P.: Minimum ... of aging, Geriatrics 21:161, 1966.
26. Walker, A. R. P.: Nutritional, biochemical and other studies on South African populations, S. Af. M. J. 40:814, 1966.
27. Ostrander, L. D., Brandt, R. L., Kjelsberg, M. O., and Epstein, F. H.: Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Mich., Circulation 31:888, 1965.
28. Ostrander, L. D.: Serial electrocardiographic ...

findings in prospective epidemiological study Circulation 34 1069 1966
29. Blackburn, H., Keys, A. Simonson, E., Ra ta harju, P and Punsar S. The electrocardiogram in population studies. A classification system, Circulation 21 1160, 1960
30. Jelliffe, D B The assessment of the nutrition status of the community Geneva, 1966, World Health Organization.
31. Van Boetzelaar G. L. and Zondag, H A. A rapid modification of the Pearson reaction for total serum cholesterol Clin. chim acta 5:943 1960
32. Goldberger E. Unipolar lead electrocardiography ed 3 Philadelphia, 1953 Lea & Febiger Publishers.
33. Gelfand, M Medicine in tropical Africa, Edinburgh, 1961 E. & S. Livingstone Ltd
34. Richardson, N J Koornhof H J and Bokkenheuser V Salmonellae and shigellae in a group of peri-urban South African Bant school children, J H g (Camb.) 61:237 1963
35. Walker A. R P Fletcher D C Reynolds, P A Bersohn, I and Sonneufeld F D Reduction to normal levels of the high ery throcyte sedimentation ates in apparently healthy Ba tu mineworkers, Nature (Lond) 177:480 1956
36. Recommended Dietary Allowances, Food and Nutrition Board, N tl. Acad. Sc N tl Res Coun Reprint Circ. Ser 1146, 1963
37. Tanner J M and Whitehouse R H. Standards for subcutaneous fat in British children, Brit. M. J 1:446 1960.
38. Hodges, R. E., and Krehl, W A Nutritional status of teenagers in Iowa, Am J Clin. Nutr 1:200 1965
39. Srikantia, S G Padmavati, S and Gopalan, C. The electrocardiogram in some India population groups, Circulation 29 118, 1964.
40. Epstein, F H., Pollack, A A and Ostrander L. D An electrocardiographic survey in Peru, Am. J M Sc. 247:687 1964
41. McPhie, J Left ventricular hypertrophy electrocardiogr phic diagnosis, Australasian Ann. Med. 7:317 1958.
42. Leatham A. The chest lead electrocardiogram in health, Brit. Heart J 12:213 1950
43. Suarez, R M and Suarez, R M J The T ve of the precordial electrocardiogram t different ag levels, Am Heart J 32:480, 1946.
44. Kaskin, L., and Brockman, L. The direction of the precordial T aves in 321 normal infants and children, Am. J M Sc 218:65 1949
45. Blackburn, H., Vasquez, C L., and Keys, A. The aging electrocardiogram A common aging process or latent coronary artery disease, Am J Cardiol. 20:618, 1967
46. Sokolow M and Lyon, T P The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart J 37 161 1949
47. Kilty S. E., and Lepeschkin, E Effect of body build on the QRS voltage of the electrocardiogram in normal men Circulation 31 77 1965.
48. Smythe P M Swanepoel, A., and Campbell J A. H The heart in k ashiorkor Brit M J 1:67 1962.
49. Boyle, D McC., and Lloyd-Jones, R L The electrocardiographic S-T segment in preg nancy J Obstet. Gynaec. Brit. C lth 73:986 1966.
50. Oram M and Holt, M Innocent depression of S-T segment and flattening of the T w e during pregnancy J Obstet. Gynaec. Brit C lth. 68 765 1961
51. Walker A R P Interpretation of biological data on one egional group may not be equally applicable to other groups, Am. J Clin Nutr 20 1025 1967
52. Vaquero, M Limon R., and Limon, A. Memorias del Segundo Congreso I ter Americano de Cardiol. 2:887 1948.
53. Seftel, H C Keeley K J and Walker A R P Characteristics of South African Bantu ho have suffered from myocardial infarction, Am. J Cardiol 12 148 1963.
54. Seftel, H C Kelley K J W lker A R. P Theron, J J and de Lange D G Coronary heart disease in aged South African Ba tu, Geriatrics 20 194 1965
55. Philips, J H and Burch G E. Cardiovascular diseases in the White and Negr races, Am J M Sc 238:97 1959
56. Coronary Heart Disease in Ad lts United States 1960-1962, N tional Center for Health Statistics, Series 11 N 10, U S Department of Health, Education, and Welfare 1965
57. Schwartz, M B Schamroth, L., and Seftel, H C. The patter of heart disease in the urbanized (Johannesburg) African, M Proc 4:275 1958
58. Snyman, H W The pattern of heart disease in Africa, M Proc 8:391 1962.
59. Schrire V Racial incidence of hypertension, rheumatic, and syphilitic disease of the heart t Groote Schuur Hospital, Cape Town, during the 10-year-period 1952 1961 S. Af M J 38:188, 1964

Character, cause and consequence of combined left axis deviation and right bundle branch block in human electrocardiograms

Thomas B. Watt, Jr., M.D., Ph.D.
Raymond D. Pruitt, M.D., M.S. (Med.)
Houston, Texas

In 1921 Wilson and Herrmann suggested the possibility that an electrocardiographic pattern characterized by a combination of extreme left axis deviation and right bundle branch block, might result from block of the anterior fascicles only of the left bundle branch together with block of the entire right bundle branch. Wilson and associates later presented three cases of right bundle branch block which were atypical in that a broad terminal S was present in Lead III. These authors then cited similar electrocardiograms in publications by Mahaim (1931) and Pardee (1933). Richman and Wolff termed such paradoxical tracings left bundle branch block masquerading as right bundle branch block. Lenegre and Lepeschkin described still other instances under the heading of bilateral bundle branch block.

Experimental supporting evidence heretofore meager has been augmented by results of investigations utilizing canine and primate hearts. In these studies, lacerations interrupting anterior fibers of the left bundle branch were produced in vivo with a ligature. The right bundle branch was sectioned with a small knife. Fig. 1 is a diagram of the interior of the canine left ventricle on which are indicated the intraventricular relationships of bundle branch divisions and typical sites of block. Standard limb, precordial, and epicardial electrocardiograms were recorded at each stage of every experiment. Block of left anterior fascicles alone caused left axis deviation in the baboon but not in the dog. Yet in both species, epicardial leads displayed similar increase in R/S ratios, delay in intrinsic deflection time by as much as 20 to 30 msec., and in some instances appearance or enlargement of a Q wave. Addition of right bundle branch block further delayed excitation of the anterior myocardium. Rapid conduction into the ventricles could then proceed only over posterior fascicles of the left bundle branch, resulting in a relatively early island of epicardial excitation posteriorly, followed by envelopment of the epicardium both laterally and medially.

From the Department of Medicine, Baylor University College of Medicine, and the Veterans Administration Hospital, Houston, Texas.
This investigation was supported in part by United States Public Health Service Grants HE-05435 (P.R.) and HE [illegible] from the National Heart Institute.
Received for publication June 17, 1968.
*Associate Professor, Department of Medicine, Baylor University College of Medicine, Houston, Texas.
**Director, Mayo Graduate School of Medicine, Rochester, Minn.

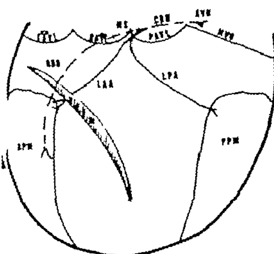


Fig 1 Sketch of the posterolateral aspect of the interior of the canine left ventricle to show the relationships of bundle branch divisions, typical sites of lacerations, and other intraventricular anatomic structures *APM* and *PPM* anterior and posterior papillary muscles *LAVL RAVL, PAVL*, left, right, and posterior aortic valve leaflets *MVO* mitral valve orifice *MS* membranous septum *AVN* and *CBH* approximate locations of atrioventricular node and common bundle of His *RBB* (broken line), right bundle branch *LAA* and *LPA* left anterior and posterior arborizations The cross-hatched area shows the typical site of ligature laceration interrupting left anterior fascicles. The dotted line represents the knife incision across the right branch on the opposite side of the septum. Mitral valve leaflets and chordae tendineae have been omitted for simplicity

as shown in Fig The mean electrical axis in both dogs and baboons then pointed in an extreme superior and anterior direction, and delays in intrinsic deflection time of more than 60 msec. were recorded in leads over the pulmonary conus region That such findings indeed represented a combination of left anterior fascicular (arborization) block and right bundle branch block was corroborated by reintroducing precisely delayed stimuli into the subendocardium at sites just distal to each of the lesions By such process, either or both of these conduction disturbances could be "corrected" at will.

These and related observations suggest, for purposes of electrocardiographic classification that the excitation process may be viewed as reaching the ventricles over a three-pronged system anterolateral (left superior) fibers, posterior (left inferior) fibers, and anteromedial (right branch) fibers. In terms of this concept six forms of intraventricular conduction disturbance may then be defined (1) left anterior fascicular block, (2) left posterior fascicular block, (3) right bundle branch block, (4) combined left anterior fascicular block and right bundle branch block (discussed herein) (5) combined left posterior fascicular block and right bundle branch block and (6) combined left anterior fascicular block and left posterior fascicular block (conventional left bundle branch block)

The purpose of the present account is to report specific electrocardiographic features and clinical findings in a series of patients who had left axis deviation combined with right bundle branch block a phenomenon found by Lasser and associates in 1 per cent of tracings recorded in a large teaching hospital.

Electrocardiographic findings

From April 1 1964 through Sept. 30 1967 a total of 59 260 electrocardiograms were recorded at the Houston Veterans Administration Hospital, of which some 15 400 (from about half that number of patients) were examined by one of the authors. In 65 patients tracings were obtained which showed unequivocal left axis deviation and unequivocal right bundle branch block, as illustrated in Fig 3 In these tracings, the following criteria were satisfied (1) left axis deviation—frontal plane electrical axis between −30° and −90° (i e Lead II predominantly negative and Lead I predominantly positive) (2) right bundle branch block—QRS complex at least 0 10 sec in duration with late R in V_1R and late S in Lead I

In 37 of the 65 patients studied Q waves diagnostic of myocardial infarction were not present. In 13 patients, a significant Q wave was present in anterior precordial Leads V R to V in 12 other patients, a significant Q wave was present in standard Leads II III and aVF The remaining 3 patients revealed Q deflections both in Leads V_3R to V and in Leads II III and aVF

Prolongation of PR interval occurred at some time in 9 of the 65 patients origi

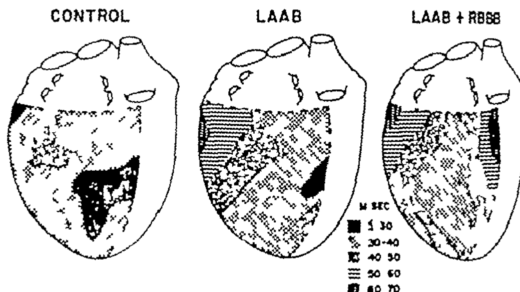


Fig. 2. Sketch of the posterior aspect of baboon heart to show stepwise elimination of earliest excitation first from an anterolateral (leftward) focus in left anterior fascicular (arborization) block, then from an anteromedial (rightward) focus in combined left anterior fascicular block plus right bundle branch block. In the last stage note the shaded band representing both lateral and medial accession from a true posterobasal site of earliest electrical activity. (Reproduced by permission of the American Heart Association, Inc., from [illegible] et al.: Circulation Res. 22:57, 1968.)

nally classified as having combined left axis deviation and right bundle branch block. Three patients showed second degree atrioventricular block. Complete (third-degree) atrioventricular block was present in 5 patients of this series. In the special case of third-degree block the diagnosis of combined left axis deviation and right bundle branch block was considered justifiable only if an identical form of QRS clearly supraventricular in origin was recorded during periods when atrioventricular conduction was present. Other arrhythmias occasionally seen were atrial fibrillation and premature ventricular contractions.

In order to ascertain possible temporal variations in the observed patterns, serial electrocardiograms were examined for many of the patients in whom unequivocal features of simultaneous left axis deviation and right bundle branch block had been detected at some time in the course of their illnesses. This portion of our investigation revealed that usually left axis deviation occurred earlier to be followed in days to months by transient or persistent right bundle branch block. In one patient however a normal electrocardiogram was followed in subsequent tracings by appearance of left axis deviation, disappearance of left axis deviation but occurrence of simple right bundle branch block, regression of right bundle branch block with recurrence of left axis deviation, and finally combined extreme left axis deviation and right bundle branch block together. Nearly two years elapsed between the tracing showing right bundle branch block alone and the first record of the combined block pattern. This patient is believed to represent distinct evidence of disease separately in both right and left bundle branches, culminating later in the bilateral effect of combined left axis deviation and right bundle branch block.

Associated clinical observations

Patients in this study were all men in the range of 45 to 78 years of age (mean 67 ± 8 years). Admission complaints were widely variable and are grouped in Table I as to whether the primary reason for coming to the hospital at that particular time was likely cardiac or noncardiac in nature. In the cardiac group the listing

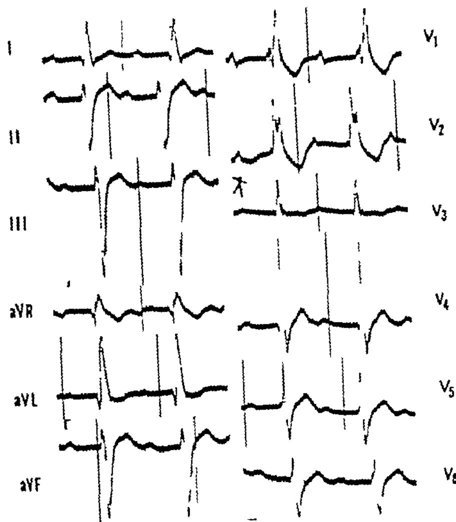


Fig. 3 Electrocardiogram showing typical features of both left axis deviation nd of right bundle branch block. Note also the presence of prolonged PR interval and the absence of diagnostic Q ves. Smallest horizontal scale divisions each represent 0.04 sec. Vertical standardization was 10 mm./mV except Lead V hich was 3 mm./mV.

for syncope/weakness included convulsive episodes in 2 patients, coma in 1 weakness in 2 and an episode of falling in 1. In the noncardiac group the listing for physical evaluation included those patients having no distressing symptoms but who were rather being examined for such purposes as compensation. The listing for other represented respiratory complaints in 2 patients psychiatric complaints in 2 and 1 patient each with night sweats and metastatic carcinoma.

Of somewhat greater interest was the compilation of data concerning association of specific cardiac findings with combined left axis deviation and right bundle branch block. Such results were gathered not alone from the single admission during which the electrocardiographic abnormality was identified but also from all other available information on each patient. Considered judgment then determined for every patient that each condition was severe moderate mild definitely absent or re

maining unknown due to lack of evidence in either a positive or negative sense. Numbers of patients were counted by category and are presented in Table II in which each horizontal row adds to 60, all of the patients whose records could be reviewed. As an example, opposite diabetes the absent column includes only those with no diabetes by history and confirmatory negative blood and urine tests as well. Opposite syncope, the mild group is composed predominantly of patients with no known loss of consciousness, but with established episodes of dizziness.

Follow-up information on these patients was in general much less than ideal. The average period of time after recognition of combined left axis deviation and right bundle branch block during which some clinical information was available, wa[s] only 6.3 months with a wide variation [?] to 46 months range, mostly skewed toward the lower intervals). Ten of the patien[ts] are known to have died at an average of 3.7 months following identification of the conduction disturbance. Autopsy was per-formed on 6 of these. Findings includ[ed] heart weight in grams of 285, 380, 500, 570, 585, and 740 with an average of [?] grams. All showed some degree of coronary sclerosis though this was minimal in the patient with the 285 gram heart, who had no history of infarction, no diagnostic Q waves, and a terminal decrease in depth of right bundle branch block. Acute an-terior myocardial infarction was [?] anatomically only in the patient having the 570 gram heart, but scarring of th[e] anterior-septal apical zones was found [in] 4 of the remaining 5 patients. The excep-tion, the patient having the 585 gra[m] heart, was noted to have some calcificat[ion] or fibrosis on pulmonary, mitral, a[nd] aortic valves. Mitral valve disease was a[lso] observed in the 285 gram heart. Papilla[ry] muscle hypertrophy was recorded [in] hearts weighing 285 and 500 grams, a[nd] left ventricular wall thickening was [ob-]served in hearts weighing 500 and [?] grams. Only 4 of the 60 patients are kno[wn] to be still alive 6 months after complet[ion] of the survey.

Conclusions

1. Experimentally induced left ante[rior] fascicular block, when combined with ri[ght]

Table I. Admission complaint

Cardiac		Noncardiac	
Symptom	N	Reason for admission	N
Chest pain	13	Orthopedic	10
Dyspnea	6	Gastroenterologic	6
Syncope weakness	6	Urologic	6
Failure	2	Physical evaluation	4
Palpitation	1	Other	6
Total	28	Total	32

Table II. Associated findings

Condition noted	Degree: Severe	Moderate	Mild	Absent	Unknown
Angina	0	13	8	27	12
Diabetes	4	7	5	16	28
Hypertension	1	15	10	21	13
Infarction	5	9	5	10	31
Syncope	3	8	13	6	30
Cardiomegaly	1	18	15	23	3
Murmurs	0	12	11	35	2

bundle branch block, produced electrocardiographic changes of left axis deviation and right bundle branch block in both canine and primate hearts.

2. Clinically a similar combination of electrocardiographic changes was encountered by the authors in approximately 1 per cent of patients on whom tracings were taken for any purpose whatsoever.

3. Among 65 patients having such electrocardiographic changes, Q waves revealed anterior myocardial scarring in 13, posterior myocardial scarring in 12, and combined anterior and posterior scarring in 3.

4. Among these 65 patients, the highest degree of atrioventricular block which could be documented was third degree in 5, second degree in 3, and first degree in 9.

5. Serial electrocardiograms revealed in these cases of combined block, that left axis deviation usually preceded by days or months the development of right bundle branch block, though the reverse sequence at times occurred.

6. Mean age of the 65 patients in the present series was 67 years of age. Only half of those presented in this article complained primarily of cardiac ailments. Pain in the chest was the most common symptom.

7. Associated clinical conditions in order of decreasing likelihood were syncope, myocardial infarction, hypertension, diabetes, and angina pectoris.

8. Necropsy on 6 of the 10 patients who are known to have died revealed a mean heart weight of 502 grams, some degree of coronary sclerosis in all, and evidence of new or old infarction in 5 of the patients.

REFERENCES

1. Wilson, F. N., and Herrmann, G. R.: Experimental study of incomplete bundle branch block and of the refractory period of the heart of the dog, Heart 8:229, 1921. Expt. 32.
2. Wilson, F. N., Johnston, F. D., and Barker, P. S.: Electrocardiograms of an unusual type in right bundle-branch block, Am. Heart J. 9:472, 1934.
3. Richman, J. L., and Wolff, L.: Left bundle branch block masquerading as right bundle branch block, Am. Heart J. 47:383, 1954.
4. Lenegre, J.: Etiology and pathology of bilateral bundle branch block in relation to complete heart block, Progr. Cardiovas. Dis. 6:409, 1964.
5. Lepeschkin, E.: Electrocardiographic diagnosis of bilateral bundle branch block in relation to heart block, Progr. Cardiovas. Dis. 6:445, 1964.
6. Watt, T. B., Jr., Freud, G. E., Durrer, D., and Pruitt, R. D.: Left anterior arborization block combined with right bundle branch block in canine and primate hearts: an electrocardiographic study, Circulation Res. 22:57, 1968.
7. Lasser, R. P., Haft, J. I., and Friedberg, C. K.: Relationship of right bundle-branch block and marked left axis deviation (with left parietal or peri-infarction block) to complete heart block and syncope, Circulation 37:429, 1968.

Hemodynamic effects of increasing the heart rate in patients with arteriosclerotic heart disease

Michael Collins, M.D.
Ami Obeid, M.D.
Gerald F. Ryan, M.D.
Harold Smulyan, M.D.
Robert H. Eich, M.D.
Syracuse, New York

Although extensively studied in normal subjects, there is little information concerning the effects of sinus tachycardia in patients with arteriosclerotic heart disease. Atrial pacing in patients without arteriosclerotic heart disease has resulted in either no change or small increments in the cardiac output until average rates of 150 beats per minute are reached when a fall in output may take place.[1,2] The purpose of this study was to determine the effect on the cardiac output of maintained sinus tachycardia produced by atrial pacing in patients with arteriosclerotic heart disease who were not in congestive heart failure.

Materials and methods

Thirteen patients to whom the study was thoroughly explained were studied. They ranged from 39 years to 72 years of age (Table I). There was no evidence of congestive heart failure by physical examination or chest x-ray. The diagnosis of arteriosclerotic heart disease was based on a history of either angina pectoris or myocardial infarction, electrocardiographic evidence of a previous myocardial infarction, or in two cases an intraventricular conduction defect. One of these had a left bundle branch block. The other patient, No. 8, subsequently died and, at postmortem examination, was found to have extensive coronary disease as well as a recent posterior and septal myocardial infarction. Two patients had systolic murmurs. One of these, No. 6, had a Grade II/VI pansystolic murmur at the apex, and by cineangiography this was shown to represent minimal mitral regurgitation. In this patient a postmortem examination revealed marked coronary artery disease as well as a large recent septal infarction. The lines of closure of the mitral valve were found to be slightly irregular due to a few homogeneous nodules. Patient No. [illegible] had an ejection murmur at the base. At autopsy showed dilatation and athero-

From the Department of Medicine, State University of New York, Upstate Medical Center, Syracuse, N. Y.

This work was supported in part by United States Public Health Service Grant No. HE 06531.
Received for publication June 28, 1968.

*Drs. Collins and Obeid were Fellows, National Heart Institute, United States Public Health Service Training Grant 5T01HE-0541.
**Present address: Rochester General Hospital, Rochester, N. Y.
***Address for reprint requests: Robert H. Eich, M.D., Department of Medicine, Upstate Medical Center, [illegible] E. Adams St., Syracuse, N. Y. 13210.

Table I. Characteristics of patients studied

Patient	Age	BSA (M^2)	Known previous infarction	Angina	Rx for CHF	Digitalis	Diabetes	Murmur	ECG	Chest x-ray cardiomegaly
1	68	2.03	0	0	0	0	+	0	LBBB	0
2	71	1.66	0	+	0	0	+	0	Nonspecific	0
3	41	1.96	+	+	+	0	0	0	Anterior wall infarction	+
4	51	2.14	+	+	0	0	0	0	Anterior wall infarction	0
5	47	1.78	+	0	+	+	0	0	Nonspecific	0
6	45	1.62	0	+	+	+	0	Mitral pansystolic	RBBB	+
7	72	1.62	+	+	+	+	0	0	Anterior wall infarction	+
8	81	1.52	0	0	+	+	0	Aortic ejection	LVE, intraventricular conduction defect	+
9	59	1.88	0	+	0	0	0	0	Normal	0
10	51	1.96	0	+	0	0	0	0	Anterior wall infarction LVE	0
11	39	1.80	0	+	0	0	+	0	Nonspecific	0
12	44	1.83	+	+	0	0	+	0	Anterior wall infarction	0
13	65	1.87	0	0	+	+	0	0	Anterior wall infarction	+

Legend: BSA, body surface area in square meters. LBBB, left bundle branch block. RBBB, right bundle branch block. Nonspecific, S-T segment and T wave abnormalities. Intraventricular conduction defect: QRS 0.12 sec. duration (not typical of RBBB or LBBB).

sclerotic changes of the ascending aorta with a normal aortic valve.

All patients were studied in the fasting state. Under local anesthesia, a No. 18 Cournand needle was inserted into the brachial artery and a No. 14 thin walled needle into the contralateral vein. The heart rate was controlled by driving the right atrium via a No. 5 bipolar battery powered electrode catheter which was passed through a No. 14 needle and directed into the right atrium under fluoroscopic control. Blood pressures were obtained by auscultation when possible. In some cases due to interference from needle placement, only systolic pressures were determined by palpation.

After resting 10 minutes in the supine position, cardiac outputs were measured via the indicator dilution technique using radioiodinated human serum albumin (RISA) and interrupted samples as described in a previous publication. The RISA was injected through a 19 gauge needle in an antecubital vein and samples were obtained from the indwelling needle in the brachial artery.

Following the control study, in six patients the atria were driven at rates of 102 to 130 beats per minute for 6 minutes and the cardiac outputs were measured. In five of these subjects, the atria were then driven for 6 additional minutes at faster rates of 170 to 138 beats per minute and cardiac outputs were obtained. Six other patients had cardiac outputs measured following 10 and 30 minutes of sustained atrial drive at a constant rate of 120 to 128 beats per minute. In three of these patients, the pacing was continued for one hour. Patient No. 13 developed a spontaneous regular supraventricular tachycardia of 130 beats per minute and cardiac outputs were obtained at 5, 10, 20, and 40 minutes during the tachycardia without pacing.

Table II Atrial drive for six minutes at two different rates

Patient	Protocol	Heart rate (beat/min)	Blood pressure (mm Hg)	Cardiac output (L/min)	Stroke volume (cc)
1	Control	72	156/80	4 53	63
	Pacing	108	155/90	5 17	48
2	Control	84	160/84	4 42	53
	Pacing	102	150/80	4 42	43
	Pacing	120	150/80	4 95	42
3	Control	84	115	5 13	61
	Pacing	102	120	5 47	54
	Pacing	120	122	4 12	34
4	Control	84	120/90	8 76	104
	Pacing	108	130	7 66	71
	Pacing	132		7 43	56
5	Control	90	120/80	4 64	52
	Pacing	120	120/80	5 15	43
	Pacing	138	110/80	4 72	34
6	Control	96	122/95	2 34	24
	Pacing	110		2 28	21
	Pacing	120		2 51	21
M	Control	85		4 97	59
	Pacing	108		5 03	45
	Pacing	126		4 75	37

Mean

Results

The response of the cardiac output to atrial drive at two different rates for a duration of 6 minutes is shown in Table II and graphically represented on Fig 1. The average ventricular rates cardiac outputs and stroke volumes in the control group were 85 ± 8 (S D) beats per minute 4 97 ± 2 09 L. per minute and 59 ± 26 ml per beat Increasing the heart rate to 108 ± 7 resulted in no change in the cardiac output (5 03 ± 2 03) and a fall in the stroke volume 45 ± 16 Although the mean outputs did not fall Patients Nos. 3 and 4 showed reductions in their cardiac outputs of 20 and 15 per cent when compared to their respective control values. The stroke volumes decreased in all patients as the heart rate increased Patient No 5 developed angina pectoris while being paced at 138 beats per minute without a fall in cardiac output.

Table III and Fig 2 represent the response of the cardiac output in six additional patients following sustained atrial drive up to a period of one hour The average ventricular rates, cardiac outputs, and stroke volumes in the control group were 81 ± 12 beats per minute, 6.19 ± 2 60 L. per minute and 75 ± 19 ml per beat. Following 10 minutes of atrial drive, the corresponding data were 121 ± 4, 6 11 ± 2 63 51 ± 22 and at 30 minutes 120 ± 7 6 22 ± 2.58 and 53 ± 23 respectively The wide range in heart rates at 30 minutes was due to Patient No. 1, who developed angina pectoris and then paced irregularly at a rate of 108 beats per minute due to frequent ectopic beats. The stroke volumes varied in an inverse relationship to the heart rate and again the mean cardiac outputs did not change. However four patients showed a 10 per cent or greater fall in cardiac output. Patients

Table III Sustained atrial d ive at a constant rate

Case	*Protocol*	*Time paced (min)*	*Heart rate*	*Blood pressure (mm. Hg)*	*Cardiac output (L./min)*	*Stroke vol me (c)*
7	Control	—	72	120	3 67	51
	Pacing	10	128	128	3 5	[illegible]
	Pacing	30	128	128	3 94	31
	Pacing*†	40	128	128	2 85	—
8	Control	—	81	180/92	4 42	63
	Pacing	10	120	172/89	3 88	32
	Pacing	40	120	180/80	3 47	29
9	Control	—	72	110	4 50	63
	Pacing	10	126	120	5 01	40
	Pacing	30	126	120	5 62	45
	Pacing	60	126	120	5 36	43
10	Control	—	103	120	10 60	104
	Pacing	10	120	110	10 57	88
	Pacing	30	120	117	10 01	83
	Pacing†	60	120	106	8 84	82
11	Control	—	90	128/83	7 60	84
	Pacing	10	120	120/90	7 39	62
	Pacing	30	120	120/90	8 59	77
	Pacing	60	120	120/90	7 20	60
12	Control	—	78	110/80	6 35	81
	Pacing	10	120	120	6 29	52
	Pacing*	30	105		5 72	53
Mean	Control	—	81	—	6 19	74
	Pacing	10	122	—	6 11	51
	Pacing	30	120	—	6 22	53
	Pacing	60	123	—	6 28	52
13	Control	—	63	—	00	32
	Spontaneous	5	130	—	3 43	26
	Supraventricular	20	130	—	3 90	30
	Tachycardia	40	130	—	3 60	28

*Angina.
†Atrial fibrillation.

Nos 7 and 10 developed atrial fibrillation after 40 and 60 minutes of pacing The cardiac output fell 22 per cent and 17 per cent in the two patients. Angina pectoris occurred simultaneously with the onset of atrial fibrillation in Patient No 7 Patient No. 12 also developed angina pectoris after 30 minutes of pacing and the output fell 10 per cent. Patient No 8 showed a slight fall in output at 10 minutes of pacing and at the end of 40 m nutes of pacing the cardiac output had decreased 1 per cent.

There was a 7 per cent increase in the cardiac output in Patient No 13 following the development of a supraventricular tachycardia and an increase in heart rate f om 64 beats per minute to 130 beats per minute Cardiac outputs recorded at 5 20 and 40 minute intervals during the tachy cardia did not vary sign ficantly

Discussion

There have been several studies evaluat ing the hemodynamic effects of atrial

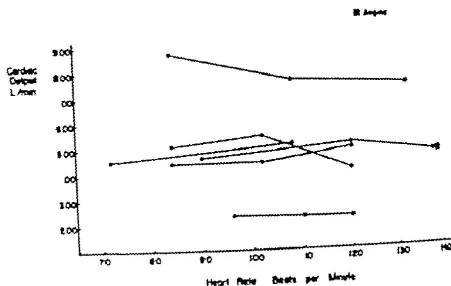


Fig 1 Sustained trial dri t different rates.

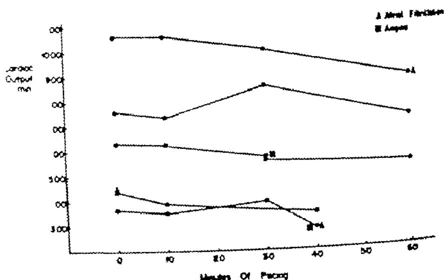


Fig 2 Sustained atrial drive at constant rate of 120 to 128 beat per minute.

pacing in patients without complete atrioventricular block.[5,7] Only a few of these consist of patients with arteriosclerotic heart disease and none to date have observed the effect of prolonged atrial pacing in this group [3]

In this study the mean cardiac outputs did not change with pacing at increasing rates of 100 to 138 beats per minute or during sustained pacing at rates of 120 to 128 beats per minute However six of the thirteen patients had falls in cardiac outputs ranging from 10 to 27 per cent. It is of interest that five of the six patients with previous myocardial infarction documented by electrocardiogram showed reductions in their cardiac outputs. Three of the six patients with falls in their cardiac outputs developed either angina pectoris, atrial fibrillation or both

In two patients the cardiac output left with the development of atrial fibrillation. During atrial pacing Haft and associates produced 26 episodes of atrial fibrillation

in three normal patients The mechanism was shown to be due to stimulation within the vulnerable period of atrial repolarization. In their study the episodes of atrial fibrillation were brief but in our patients atrial fibrillation persisted for several hours after pacing was stopped The differences noted may have been related to the fact that our patients had heart disease The heart rates following the onset of atrial fibrillation were comparable to the ventricular rates during sustained atrial drive in our patients. This would suggest that loss of the atrial contribution to ventricular filling was responsible for the fall in cardiac output that occurred in these patients.

In the other four patients whose cardiac outputs fell shortened diastolic filling times, secondary to rapid heart rates, could be responsible in part for the decrease in output that occurred An additional explanation would be the inability of the impaired coronary circulation to supply sufficient flow for adequate myocardial oxygenation at these heart rates. Wégria and associates[11] and Laurent and co-workers,[12] using the anesthetized open chested dog and electrical stimulation to increase the heart rate showed that coronary flow and myocardial oxygen consumption increased as the heart rate increased Sarnoff and associates, with the isolated supported heart preparation in the dog showed that tension time index per minute may be used to estimate myocardial oxygen consumption in the nonfailing heart. Using this measurement to reflect oxygen utilization by the heart, Sowton and coworkers, paced twenty two patients with ischemic heart disease for short periods. The level of tension time index per minute at which angina pectoris occurred was reproducible within 5 per cent for each patient. Frick and associates, by giving their patients nitroglycerine prior to pacing were able to reduce the tension time index and the patients then did not develop angina pectoris at heart rates that previously produced pain.

In Sowton's series, fifty episodes of angina pectoris occurred with only four of these resulting in a fall in cardiac output of greater than 1 liter per minute We observed three episodes of angina pectoris with pacing In the two patients who remained in sinus rhythm one showed a fall of 10 per cent and in the other the cardiac output remained stable It is of interest that in Sowton's series if angina pectoris did not occur within the first 45 seconds of pacing it would not occur even though pacing was continued for several minutes at that rate In contrast, the three episodes of angina pectoris in our study followed 6 30 and 40 minutes of pacing

Three other patients who did not develop angina pectoris or atrial fibrillation during pacing also showed a fall in cardiac output of 1 liter per minute or more Two of these three patients had electrocardiographic evidence of a previous myocardial infarction. With this degree of heart disease even though angina pectoris did not occur myocardial oxygen demand in excess of availability could explain the fall in cardiac outputs noted

Summary

The hemodynamic effects of pacing the right atrium to produce sinus tachycardia of moderate degree for sustained periods were studied in thirteen patients with arteriosclerotic heart disease Although the mean remained stable, the cardiac outputs fell in six patients. In five of these, the fall in cardiac output was one liter per minute or more. In addition, five of the six patients showed electrocardiographic evidence of a previous myocardial infarction. Two patients developed atrial fibrillation during pacing and did not return to sinus rhythm until several hours after pacing had been stopped Possible mechanisms for the changes in cardiac outputs noted have been discussed Our data suggest that tachycardias of moderate degree may produce a reduction in the cardiac output, or angina pectoris in patients with arteriosclerotic heart disease.

REFERENCES

1 Benchimol, A. Cardiac functions during electrical stimulation of the heart. Effect of exercise and drugs in patients with permanent pacemakers, Am J Cardiol 17:27 1966.
2 Benchimol A., Ellis, J G and Dimond, E. G Hemodynamic consequences of atrial and ventricular pacing in patients with normal and

abnorm l hearts. Effect of exercise at a fixed t ial and entricular rat Am J Med. 39:911 1965
3 Stein E Damato, A N Kosowsky B D Lau, S H and Lister J W The relation of heart rat t cardiovascular dynamics Pac ng by trial lectrodes, Circulation 33:925 1966
4 Ross, J Linhart J and Br unwald E Effects of hanging heart te man by elec trical t mulation of the right t rum Studies t rest during exercise nd with isopr terenol Circulation 32:549 1965
5 St in, E D mato A N Kosowsky B D Lau S H and Lister J W Cardiovascular response t alterations in heart t bove and below the t Am J Cardiol 17 140, 1966
6. Cobb F A Th pson J J Nolan J J and Short F A Ch onot opic lter tion in cardiac perform nce m Ci Res 11:241 1966
7 Samet P C stillo, C Bern tein W H and Fernandez, Pedr Hemodynamic result of right atrial pac ng 33 ormal subjects, Di Chest 52:653 1967
8 Fich R F J t rs R J Cuddy R P Sm l an H nd L ons R H The hemodynamic l l le h pe t sion Am Heart J 63 188 196
9 Sowton, G E., Balcon, R Crow, D a Frick M H Measurements of the ang threshold using atrial pacing, Cardiova Re 1:301 1967
10 Frick, M H Balcon, R., Crow, D and Sow ton, E. Hemodynamic effects of nitroglyce in patients with angina pectoris studied by atrial pacing method, Circulation 37:160, 19
11 Haft J I Lau, S. H Stein, E., Kosowsk B. D and Damato, A. N Atrial fibrillat produced by atrial stimulation, Circulat 37 70 1968.
12. Wégria Réne Fra k C. W Wang, H and Lammerant, J The effect of atrial a ventricular tachycardia on cardiac outp coronary blood flow and mean arterial bl pressure Circulation Res 6:624 1958
13. Laurent D Bolene-Williams, C., William L. and Katz, L. N Effects of heart rate coronary flow and cardiac oxygen consumpti Am J Physiol. 185:355 1956
14 Sarnoff S J Braunwald, E Welch, G Case R. B Stainsby W N and Macruz, Hemodynamic determinants of oxygen c sumption of the heart with special referenc the tension-time index, Am. J Physiol 192: 1958

Clinical observations on a new antihypertensive drug, 2-(2, 6-dichlorphenylamine) 2 imidazoline hydrochloride*

*Guido Smet, M.D.***
S. W. Hoobler, M.D.
*Shafeek Sanbar, M.D.****
Stevo Julius, M.D.
Ann Arbor, Mich.

Establishing an effective therapeutic regimen in cases of severe hypertension continues to be a highly individualistic process of balancing side effects against blood pressure response. Sympathetic blocking agents needed in most cases of severe hypertension often disable the patient by causing an orthostatic hypotension as the price he must pay for a partial reduction of recumbent blood pressure.

During the past several years a new antihypertensive agent, 2-(2,6-dichlorphenylamine)-2-imidazoline hydrochloride (Catapres) has been under clinical study. The mode of action of this drug has not yet been defined,[1] but it has been shown to be effective and relatively safe with drowsiness as its major side effect. Most important, the new agent is reported to lower recumbent and standing blood pressures equally well throughout the day without the wide diurnal variations that induce excessive orthostatic hypotension when the patient rises in the morning but it fails to prevent nocturnal recumbent hypertension. Although metabolic side effects from Catapres have not been noted in clinical reports, a slight diabetogenic tendency has been observed in some species of animals.

The study reported here was designed toward three specific objectives: (1) to test the agent alone in subjects with mild hypertension in order to examine its reported ability to lower recumbent blood pressure without creating postural hypotension, (2) to test long-term efficacy and acceptability of the agent for severely hypertensive patients intolerant of conventional sympathetic blocking agents, (3) to evaluate the frequency and acceptability of various side effects and to examine the drug's effects on liver and hematopoietic function and on carbohydrate metabolism.

From the Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Mich. 48104. Requests for reprints should be directed to this address.

The Clinical Research Unit, University of Michigan Hospital, has assisted greatly in this investigation under Grant 1MO1-FR-[illegible] from the Department of Health, Education and Welfare, United States Public Health Service.
Received for publication Jul [illegible] 1968.

*Kindly supplied by Dr. Fred A. Kennedy, Jr., Geigy Pharmaceuticals, Ardsley, N. Y.

**Present address: 73 Molenbaan, Dessel, Belgium.
***Advanced Research Fellow, American Heart Association.

Methods

Sixteen patients ranging in age from 27 to 65 years were studied They were divided into two groups on the basis of relative severity of hypertension Group 1 included 6 patients with mild blood pressure elevation who had recorded their blood pressure at home for several weeks preceding the drug trial These patients were given Catapres alone for a period of one month the studies being directed chiefly at the effects of the drug on carbohydrate metabolism Group 2 comprised the remaining 10 patients who had had severe postural hypotension or were otherwise refractory to treatment with the usual sympathetic blocking agents. Background diuretic therapy was maintained in all these patients, who were treated with Catapres alone for periods of 5 to 11 months. All the patients were admitted to the Clinical Research Unit of the University of Michigan Hospital for the initiation of Catapres treatment and were discharged in 5 to 6 days

Carbohydrate tolerance was tested in subjects belonging to Group 1 as follows

Prior to hospital admission they were placed on a 300 Gm carbohydrate diet for three days. After admission, the tolbutamide tolerance test and the intravenous glucose tolerance test were performed Then an oral test dose of Catapres, 0 150 mg was given and the effects on blood pressure were noted. Based on the response observed an appropriate treatment regimen was established and the tolbutamide test was then repeated on the fourth or fifth day of therapy in the hospital The individual's glucose tolerance was re-examined on the second day of inpatient treatment and at the end of a month of outpatient treatment with Catapres, three days after the preparatory diet had been reinstituted The intravenous test dose was administered in the morning in the fasting state, two hours after drug ingestion

The more severely hypertensive subjects belonging to Group 2 were handled as follows. After other antihypertensive drugs, except diuretics, had been discontinued an oral test dose of Catapres was administered and subsequent dosage …

Table 1 Effect of dichlorophenylamine imidazoline (Catapres) on blood pressure initially and after one month

Case No.	Patient age	Inpatient BP (mm Hg)				Change in morning home blood pressures* (mm. Hg) (Average of last 5 days compared to pretreatment status)		Daily dose (mg)
		Last BP before test dose		Maximum decline with first test dose 0.150 mg		1 month after drug		
		R	S	R	S	R	S	
1	65	180/110	165/100	−20/−15	−20/ 0	+ 8/−22	+13/− 8	0 175
2	50	150/100	135/110	−35/−20	−25/−15	Discontinued†		0 150
3	48	170/100	140/105	−45/−20	−20/−35	+ 5/−12	+ 1/− 7	0 225
4	27	185/125	165/125	−40/−30	−55/−30	−41/−16	−38/−25	0 300
5	38	195/145	165/130	−55/−55	−35/−25	−21/−15	− 6/− 7	0 300
6	49	195/125	205/103	−45/−30	−55/+ 7	+13/+ 3	+ 5/− 3	
Average changes				−40/−28	−35/−16	− 7/−12	− 5/−10	

*Average of last 5 readings at home in pretreatment phase compared to last 5 morning readings at home before returning to clinic one month. Blood pressure taken in recumbency (R) or standing (S)

†Complained of drowsiness and depression. Drug discontinued before return visit.

Table II. Effect of Catapres on carbohydrate metabolism

Case No.	Fasting blood sugar						Daily dose (mg.)	Intravenous glucose tolerance test. Change in K value after Catapres†	
	Related to test dose*				On therapy				
	Before		After		+3-4 days	+30 days			
	−2 day	−1 day	2 hrs	+1 day				1 day	30 days
1	96	96	90	74	90	80	0 375	−0 03	−0 19
2	83	80	98	95	80	—	0 300	+0 19	—
3	92	80	82	74	78	70	0 150	−0 02	−0 11
4	82	78	76	84	82	81	0 375	+0 09	+0 31
5	80	82	78	85	75	—	0 300	+0 26	—
6	88	75	80	80	80	90	0 300	−0 16	−0 03
Mean	86 8	81 8	84 0	82 0	80 8	80 3	0 300	+0 06	0 00
Sign $p < 0.05$	NS	NS	NS	NS	NS	NS			

*Fasting blood sugar drawn 2 hours after oral administration of drug. Test dose of drug was 0 150 mg

†K value expresses the slope of disappearance of the glucose solution (25 mg. per kilogram) injected at time "0". Samples taken at 10, 20, 30, 40, 50, and 60 minutes. A negative change in K value denotes slower rate of removal of administered glucose. Changes observed are within the limits of normal variation.

Table III. Replacement of conventional drugs with Catapres in severely hypertensive patients

Case No.	Pretreatment Hospital admission BP recumbent	Status of blood pressure							Principal side effects	
		On usual drug therapy*			On Catapres					
		Outpatient BP		Daily dose (mg.)	Outpatient BP		Duration on Catapres (mo.)	Daily dose (mg.)		
		Recumbent	Standing		Recumbent	Standing			Usual drug	Catapres
Guanethidine										
7	230/140	190/136	100/70	100	175/130	182/140	8	0 900	A.M. syncope	Constipation
8	220/130	222/123	118/85	75	183/125	192/132	7	0 800	A.M. syncope	Constipation
9	200/170	190/100	160/100	50	146/94	120/80	10	0 900	Diarrhea	0
10	220/140	228/130	140/100	100	222/125	195/125	3†	1 200	A.M. syncope	0
11	250/160	215/115	205/130	100	122/88	180/150	10	0 400	None	0
Alpha-methyldopa										
12	240/138	200/130	170/104	1 500	134/88	142/84	11	0 800	A.M. syncope	Drowsiness
13	215/130	240/110	190/124	1 600	194/102	167/108	10	0 600	Dizziness	Drowsiness
14	205/130	196/100	174/120	1 500	180/100	192/108	11	1 200	None	None
15	240/130	195/112	190/114	2 000	161/104	140/104	7	0 825	Fatigue	None
Reserpine										
16	240/130	196/100	109/106	0 25	168/105	135/95	8	0 700	Depression	None

*All patients received maximally effective dosage of thiazide or chlorthalidone throughout the study.

†Blood pressure uncontrollable with Catapres alone. Trial discontinued after 3 months.

We wish to express ou appreciation t Miss Alice Waralmki, R.N Hypertension Clinic, for assistance in data collection and analysis and to Mr Stephen Mitchell for assistance in the meta bolic studies cited.

REFERENCES

1 Bock, K. D Hermsoth V Merguet P and Schroenermark J Clinical and clinical-experimental studies w th a new hypotensive agent dichlorophenyl-amino imidazoline (DCI) Deutsch. Med. Wchnschr 91 1761, 1966

2. Nayler W G Rosenbaum, M Mcinnes, I, and Lowe T E. Effect of a new hypotensive drug, ST 155, on the systemic circulation, AM HEART J 72 764 1966.

3. Hoefke, W and Kobinger W : Pharmacologic effects of 2 (2,6-dichlorophenylamino)-2-imidazoline hydrochloride, a new antihypertensive substance Arzneimittelforsch. 16 1038, 1966

Electrocardiographic and serum enzyme changes in subarachnoid hemorrhage

David Hunt M.D M.R.A C.P
Colin McRae M.B M.R.C.P F.R.A.C.P
*Peter Zapf B Sc.****
Victoria Australia

In 1947 Byer and co-workers[1] reported large upright T waves and Q-T interval prolongation in the electrocardiogram (ECG) of a patient with a subarachnoid hemorrhage, and Levine[2] in 1953 described a 69-year-old woman with a subarachnoid hemorrhage whose ECG initially showed widespread T wave inversion and later ST segment elevation in Leads V_{1-4}. Autopsy showed a ruptured aneurysm of the circle of Willis, but the heart was considered normal. Since then there have been numerous case reports of electrocardiographic changes seen in association with subarachnoid hemorrhage. The changes which may be seen include ST-segment displacement, T wave changes, Q-T interval changes, prominent U waves, and supraventricular arrhythmias. Changes in T waves and ST segments suggestive of ischemia are said to occur in about 40 per cent of subarachnoid hemorrhages. The mechanism of the electrocardiographic changes is unknown but hypokalemia, lesions involving area 13 on the orbital surface of the frontal lobes, or actual myocardial involvement[3] have been suggested as possible factors. It has been our impression that significant electrocardiographic changes in subarachnoid hemorrhages are less frequent than previously reported and this prospective study was made to determine the frequency of changes and to assess some of the factors that may have caused them.

Clinical material and methods

Twenty patients (twelve men and eight women) with primary subarachnoid hemorrhage admitted to the public wards of The Royal Melbourne Hospital between April and December 1967 have been studied. We have excluded patients with subarachnoid bleeding secondary to intracerebral hemorrhage and any patients with known heart disease or hypertension. Diagnosis of subarachnoid hemorrhage was based in each patient on the typical clinical presentation and was confirmed by lumbar puncture. Total cerebral angiography was performed in each patient. Standard 13 lead ECG's, serum creatine phosphokinase (CPK) and serum glutamic oxaloacetic transaminase (SGOT) estimations were performed on each patient on admission and were repeated every two to three days,

From the Departments of Cardiology and Biochemistry, The Royal Melbourne Hospital, Victoria, Australia.
Received for publication July 12, 1968.
*National Heart Foundation Research Fellow in receipt of Grant in Aid No. G[illegible].
**Assistant Physician, Cardiac Department.
***Biochemist.

if possible until the results of the tests became normal or the patient died or was operated on. In our laboratory upper limits of normal for CPK and SGOT are 70 U and 35 U respectively. Serum potassium levels were determined on admission and arterial pCO_2 was estimated by the rebreathing method to assess the presence of hypoventilation. Two patients (cases 14 and 16) died. Autopsies confirmed the aneurysms seen on angiography and showed bilateral frontal lobe destruction and blood in the cerebral ventricles in each instance. The hearts weighed 350 and 330 grams respectively and the coronary arteries showed minimal involvement with atheroma. No macroscopic or microscopic abnormalities were seen in the myocardium.

Results

A clinical summary of the patients is shown in Table I. Table II shows the incidence of electrocardiographic abnormalities and Table III details enzyme changes in those patients with abnormal enzyme levels.

Eight patients showed minor but definite T wave changes being either flattening or notching. In two patients (cases 11 and 17) definite T wave inversion occurred. The tracings of patient 11 showed QT prolongation and T wave inversion in V associated with T wave flattening in Lead I (Fig 1 A). These changes were still present on the eleventh day but an ECG seven months later (Fig 1 B) showed no abnormality. The tracing on the second day after patient 17's hemorrhage showed T wave inversion in Leads I aVL and V associated with ST-segment elevation in V. The next day the tracing showed even more marked symmetrical T wave inversion over the chest leads but the ST segments had returned to normal (Fig 2 A). The T waves returned to normal by the ninth day (Fig 2 B) and no pathological Q waves were seen. The changes were associated with marked bradycardia and nodal escape beats.

Prominent U waves were seen in two patients (cases 12 and 16) but in neither of these was the U wave considered to be abnormal. Those in patient 12 were present only on the second day while those in patient 16 remained until death on the ninth day.

Five patients showed an increase in the QT interval[4] but in no case was the interval abnormally short.

Sinus bradycardia occurred in six patients and was associated with a wandering atrial pacemaker in two patients (cases 4 and 5).

In nine of the twelve patients with abnormalities in the ECG the changes were present on admission and seven of these nine patients had been admitted within two days of the onset of the hemorrhage. The minor T wave changes in patients 1 and 5 developed between the fifth and seventh days while the wandering atrial pacemaker in patient 4 developed on the third day.

Of the twelve patients with abnormal ECG's, the tracings had returned to normal by the seventh day in four patients and in another six by the eleventh day. In patient 11 the changes were still present on the eleventh day but were absent seven months later. Patient 16 died on the ninth day with persistently abnormal ECG's.

In all our patients, serum potassium on admission and at later times was within the normal range for our laboratory (3.5 to 5.5 mEq per liter).

The arterial pCO_2 estimated by the rebreathing technique was not raised in any of our cases (normal upper limit in our laboratory is 45 mm Hg). Six of the seven patients with arterial pCO_2 values less than 35 mm Hg had abnormal ECG's while six of the thirteen patients with pCO_2 levels over 35 mm Hg had abnormal ECG's.

Electrocardiographic abnormalities were present in each of the three patients who were drowsy on admission (patients 1, 5 and 17) but in only nine of the seventeen patients who were alert on admission.

Total cerebral angiography was performed in all patients and only five showed no abnormality. In those patients in whom multiple aneurysms were found the source of bleeding could be determined (by demonstration of a local space-occupying lesion by local vascular spasm or directly at operation) in all except patient 11. This woman had one aneurysm on the bifurca

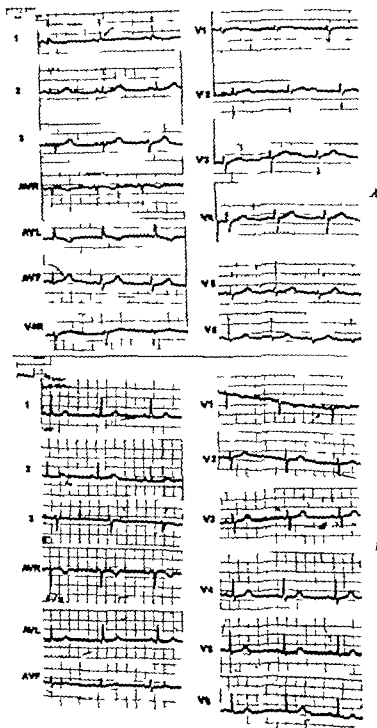


Fig. 1 Electrocardiogram of case 11 (*A*) on admission and (*B*) seven months later

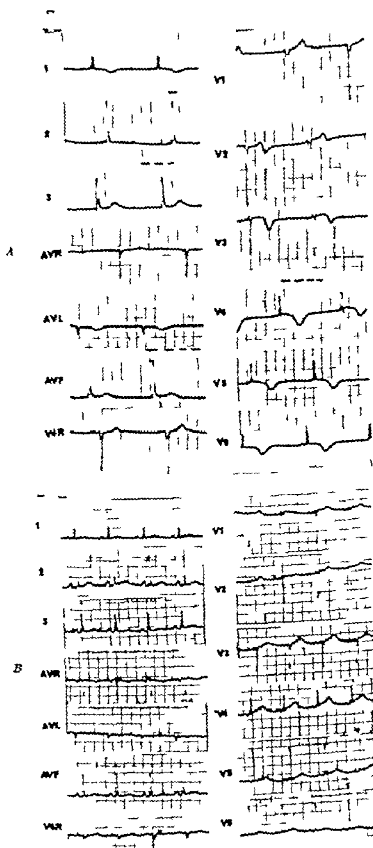


Fig. 2. Electrocardiogram of case 17 (A) on the third day and (B) on the ninth day.

Table I. Clinical summary of patients

N	Sex	Age	State on admission	pCO	Day of first ECG	Site of aneurysm	ECG	Enzymes	Clinical progress
1	F	18	Drowsy	37	1	Internal carotid	Abnormal	Abnormal	Carotid artery ligation on day 7
2	M	22	Alert	29	7	Posterior communicating	Normal	Normal	Carotid artery ligation on day 9
3	M	35	Alert	32	1	Cerebellar angioma	Abnormal	Normal	Uneventful
4	F	25	Alert	30	2	None seen	Abnormal	Abnormal	Uneventful
5	M	31	Drowsy	34	2	Anterior communicating	Abnormal	Abnormal	Aneurysm clipped on day 14
6	M	22	Alert	38	2	Frontal cortical vascular malformation	Normal	Normal	Frontal lobectomy on day 9
7	F	44	Alert	36	1	Division of middle cerebral	Abnormal	Normal	Uneventful
8	F	36	Alert	34	9	None seen	Abnormal	Normal	Uneventful
9	F	38	Alert	44	9	None seen	Normal	Normal	Uneventful
10	M	28	Alert	40	3	Division of middle cerebral	Normal	Abnormal	Uneventful
11	F	46	Alert	38	1	Anterior communicating (site of bleeding) Bifurcation of basilar	Abnormal	Normal	Uneventful
12	F	35	Alert	40	1	Posterior communicating Internal carotid	Abnormal	Normal	Uneventful
13	M	25	Alert	40	1	Division of middle cerebral	Normal	Normal	Uneventful
14	M	43	Alert	40	1	Anterior communicating	Normal	Abnormal	Well, until became comatose and hemiparetic on day 5, died day 7
15	M	55	Alert	36	1	Anterior communicating	Abnormal	Abnormal	Uneventful
16	M	45	Alert	38	1	Anterior communicating	Abnormal	Abnormal	Deteriorated on day 7 died day 9
17	M	49	Drowsy	32	1	Division of middle cerebral (site of bleeding). Anterior communicating	Abnormal	Abnormal	Improved slowly to frontal leucotomy-like state
18	F	30	Alert	40	1	None seen	Normal	Normal	Uneventful
19	M	43	Alert	32	3	Anterior communicating	Abnormal	Normal	Anterior cerebral artery tied on day 9
20	F	42	Alert	40	1	None seen	Normal	Normal	Uneventful

Table II Incidence of electrocardiographic changes

ECG change	No. of cases	Incidence
T wave flattening	8	Cases 3 5, 7 8, 12, 15 16, 19
T wave inversion suggestive of ischemia	2	Cases 11 17
QT prolongation	5	Cases 1 4 5 11 17
U waves > 1 mm	2	Cases 12 16
ST-segment changes	2	Cases 17 19
Wandering atrial pacemaker	2	Cases 4 5
Sinus bradycardia	6	Cases 2, 5, 6 7 11 17

Table III Enzyme levels in patients with abnormal enzyme levels

Case No.	Day												
	1	2	3	4	5	6	7	8	9	10	11	12	13
CPK Units													
1		91		99		34					50		
5			45		322		266		67				169
10									290				
15		83	71			335		111					
16		262	256		218								
17		193	944		1080								
SGOT Units													
4		44		48		72					40		
5			28	28	82		48		52				[illegible]
10									54				
14		92		76			80						
17		58	92		184								

tion of the basilar artery and another on the anterior communicating artery We have considered her source of bleeding to be the anterior communicating aneurysm as this is the most likely situation.[7] Electrocardiographic abnormalities occurred in nine of the thirteen patients (69 per cent) in whom the source of bleeding was in the anterior cranial fossa and in three of the seven patients (43 per cent) in whom either no lesion was seen or the source of bleeding was outside the anterior cranial fossa.

Eight patients had raised enzyme levels six having raised CPK five having raised SGOT and three patients having both enzymes raised. Abnormal enzyme levels were present in six of the twelve patients with abnormal ECG's, but in only tw of the eight patients with normal ECG' The enzymes became abnormal by th second day in some patients (cases 1 16 and 17) but not until the fifth day i another patient (case 5) Maximum level occurred as early as the second day i patient 16 or on the sixth day in patient 1 Abnormal levels still persisted on th seventh day in four patients in whom est mations were performed at this time.

Discussion

The occurrence of electrocardiograph changes in association with subarachno hemorrhage is of practical importance, b cause such changes may simulate those myocardial infarction or ischemia. Path

Table IV. Incidence and types of electrocardiographic changes

Authors	*Total No. cases*	*No. of cases with electrocardiographic changes*
Cropp and Manning[4]	29	T changes in I, V_L, V... suggestive of infarction or ischemia (15) ST changes suggestive of infarction (11)
Hersch	20	T inversion V[illegible] (4) ST elevation (5)
Shuster[3]	12	T depression or inversion V[illegible] (7) ST depression (2)
Present series	20	Minor T changes (8) T inversion suggestive of ischemia (2)

logical Q waves have not been described as a feature of the ECG of subarachnoid hemorrhage and this point may be helpful in differentiation. In one reported case[2] surgery for intracranial aneurysm was delayed because of an electrocardiographic pattern suggesting myocardial infarction. Death occurred from recurrent hemorrhage and autopsy showed a normal heart. Changes in this patient were confined to the T waves and ST segments. The difficulties in diagnosis are increased by the fact that acute myocardial infarction may occur in association with subarachnoid hemorrhage.[5] Our results indicated that estimations of SGOT and CPK are of limited help in resolving this problem.

T wave inversion or depression is common in subarachnoid hemorrhage (Table IV) but occurred in only 10 per cent of our patients. The difference in incidence may be due to the inclusion of patients with cardiac disease in the other series, as five of Cropp and Manning's[4] fifteen patients had either hypertension or symptoms of heart disease and three of Shuster's patients had hypertension. However, our patients and those of Hersch were selected and did not include any with known heart disease or hypertension. Large wide upright T waves[3,4] and tall pointed T waves have been described in association with subarachnoid hemorrhage but these changes were not seen in our series nor in those of Cropp and Manning[4] or of Hersch.

Abnormal U waves occur in 27 to 60 per cent of patients[3,4] but in our series only two patients (cases 12 and 16) showed prominent U waves, and in neither of these was the U wave considered to be abnormal.

QT interval prolongation[4] occurred in only 25 per cent of our patients, while this was as high as 40 per cent in other series,[3] and although QT interval shortening has been reported as occurring in 17 per cent of patients, none of our patients showed this abnormality.

Sinus bradycardia was common among our patients, as in patients in other series.[3]

The resolution of abnormal electrocardiographic changes is similar to the experience of Shuster[3] who followed eight of his patients with serial ECG's and found that the changes returned to normal within two days in two patients, seven days in another two patients, and fourteen days in another patient. However, changes still persisted in the other three patients for 17, 35, and 45 days, respectively, while in our series abnormalities persisted for more than eleven days in only one patient.

Possible causes of the electrocardiographic changes include hypokalemia, changes in blood gases, autonomic dysfunction, and focal myocardial necrosis.

Hypokalemia was found to be present in 50 per cent of the patients in one series[4] and it was suggested that this might be important in the causation of electrocardiographic changes. However, our patients and those of others all had normal serum potassium levels and the changes seen in subarachnoid hemorrhage are quite unlike those of hypokalemia.

Anoxia may cause T wave changes[5] None of our patients had clinical signs suggesting a low cardiac output and none had symptoms of lung disease Three patients were drowsy on admission and these all had electrocardiographic changes while only nine of the seventeen patients who were alert on admission had these changes. It has been shown that as the level of consciousness deteriorates the number of electrocardiographic abnormalities per person increases both in subarachnoid hemorrhage[1] and in head injuries.[5] Arterial pCO_2 levels by the rebreathing technique were performed to determine if hypoventilation was present In no case was the pCO above normal limits and thus hypoventilation is unlikely to have been the cause of the electrocardiographic changes. We did not assess the presence of causes of hypoxia associated with normal or low pCO_2 levels It is interesting to note that whereas six of the seven patients with pCO_2 level less than 35 mm Hg had abnormal ECGs only six of the thirteen patients with pCO levels over 35 mm Hg had abnormal ECGs Alkalosis can cause T wave flattening or ST segment depression but the changes seen in subarachnoid hemorrhage are not those typical of alkalosis and it is considered unlikely that the slight reduction in levels of pCO_2 that we observed could cause electrocardiographic changes. However the low levels may be a response to hypoxia which has caused the electrocardiographic changes or the result of hyperventilation due to brain damage or irritation Elucidation of the relationship of blood gas changes and electrocardiographic abnormalities requires further investigation

The autonomic nervous system has been implicated in the causation of the electrocardiographic changes It has been suggested that the changes are due to lesions in the vicinity of area 13 the cortical representation of the vagus nerve on the orbital surface of the frontal lobe, and some of the features of the electrocardiographic changes seen in association with subarachnoid hemorrhage resemble those of vagal stimulation. Experimentally in dogs it has been shown that transient vagal stimulation increased T wave amplitude[13] and that prolonged stimulation of the vagus leads to negative T waves and ST depression.[1] Other workers[14] have shown in dogs that vagal stimulation for 31 to 45 hours leads to areas of capillary congestion and hemorrhage in the heart and early hyaline degeneration of myocardial fibers. This damage can be prevented by atropine and is accentuated by eserine. Atropine can cause the return of depressed ST segments to the isoelectric line in man with subarachnoid hemorrhage. If the electrocardiographic changes are in fact due to interference with cortical area 13 we would expect those aneurysms associated with the electrocardiographic changes to be mainly in the anterior cranial fossa. Cropp and Manning[2] found that the site of the bleeding aneurysm was in the anterior cranial fossa in 73 per cent of their patients with electrocardiographic abnormalities, but it has been shown that 63 per cent of all patients with subarachnoid hemorrhage have their aneurysms in the anterior cranial fossa.[15] Of our twenty patients, 62 per cent had bleeding aneurysms in the anterior cranial fossa and of these, 69 per cent had electrocardiographic abnormalities, while abnormalities occurred in 43 per cent of those patients in whom the source of bleeding was not in the anterior cranial fossa. It is therefore apparent that interference with area 13 is not the only important factor in causing the electrocardiographic changes.

Sympathetic stimulation can also cause some of the features seen in the ECG of subarachnoid hemorrhage. Stimulation of regions of the ventral hippocampus and medial nucleus of the amygdala in animals[4] can lead to inversion and increased amplitude of T waves, prolonged QT intervals, and alteration in ST segments which can be reversed by midcervical cord transection thus interrupting the sympathetic connections. Alterations in the sympathetic tone of the heart caused by excision or stimulation of the stellate ganglion produces Q-T and T wave changes similar to those seen in subarachnoid hemorrhage.[17] Right-side sympathetic overactivity produced by excision of the left ganglion or right side stimulation produced increased T negativity without Q-T changes while left side overactivity caused increased Q-T intervals and increase in

the T-wave amplitude. Although there is considerable overlap in the sympathetic innervation of the heart the left stellate ganglion supplies most of the posterior wall and the right stellate ganglion the anterior wall of the ventricles. As electrocardiographic changes are more commonly seen in the anterior leads than in the posterior leads of the cardiogram, the sympathetic distribution may be of importance. T wave and ST-segment changes similar to those seen in subarachnoid hemorrhage and lasting 7 to 10 days can be induced by infusing epinephrine into the left coronary artery of dogs.[8] Prolonged stimulation of lateral areas of the hypothalamus enhanced the development and persistence of ischemia-like electrocardiographic changes in cats, and bilateral stimulation caused small hemorrhages and infarction of myocardial fibers. All this experimental work is compatible with the thesis that autonomic imbalance may play a part in the causation of the electrocardiographic changes seen in man with subarachnoid hemorrhage. The presence of subendocardial hemorrhage in the hearts of three patients dying after subarachnoid hemorrhage in whom the ECG's were abnormal[3] led to the suggestion that the electrocardiographic changes are caused by cardiac injury or ischemia, but other workers[illegible] have failed to confirm these findings. The difference may perhaps be explained by the diligence displayed in seeking myocardial damage. Connor[illegible] after a careful study claimed that myocardial damage can be detected in patients dying early after subarachnoid hemorrhage, and that foci of myocytolysis can be found in the hearts of those who survive four to seven days, providing a sufficient number of histological blocks are examined.

If the electrocardiographic changes were due to myocardial damage, one would expect some correlation between such changes and serum enzyme abnormalities. We found raised enzyme levels in six of the twelve patients with abnormal ECG's, but in only two of the eight with normal tracings. The magnitude or time course of the electrocardiographic and enzyme changes in general showed some correlation. Certainly case 17 had the most abnormal ECG and the highest enzyme level the enzymes reaching maximum values on the fifth day and the electrocardiographic changes being most marked on the third day. Case 11 however also had marked electrocardiographic changes and yet the enzymes were normal. In general, the electrocardiographic abnormalities preceded the enzyme peaks by two or three days.

The levels of SGOT seen following subarachnoid hemorrhage are only occasionally sufficiently elevated to suggest myocardial infarction however the CPK levels may be such as to cause diagnostic difficulty. In such patients, the time pattern of enzyme elevation is likely to be helpful. In myocardial infarction levels rise within six to twelve hours, reach a maximum in one to two days, and have usually returned to normal in three to six days. In subarachnoid hemorrhage, the levels may be abnormal on the second day but may not rise until the fifth day. Maximum levels may occur as early as the second day or as late as the sixth day, and abnormal levels may persist past the seventh day and this pattern would be consistent with myocardial lesions developing slowly over the first four days. No alternative cause for SGOT elevation was apparent in any of our patients. None was in shock and there was no clinical evidence of liver disease. Liver function tests were performed in only two of the patients with elevated SGOT levels and were normal in each case.

While accepting the thesis that myocardial damage may occur in association with subarachnoid hemorrhage, it is difficult to believe that this damage would be sufficient to produce enzyme levels such as those found in case 17. Dubo and associates,[illegible] using isoenzyme studies, showed that CPK was mainly of muscle rather than brain origin and they suggested that the raised levels may be a complex response of the whole organism rather than a consequence of enzyme release from one particular locus of necrotic cells. While this is not an entirely satisfactory explanation we find it difficult to suggest anything more exact at this stage.

It seems likely to us that the electrocardiographic changes in subarachnoid hemorrhage are due to autonomic im

balance resulting from irritation or depression of vagal or sympathetic centers or their pathways. Prolonged or severe imbalance may result in the development of focal myocardial lesions and these may be responsible at least in part for the enzyme levels obtained. It is unlikely however that these lesions account entirely for the enzyme elevation or that they play a major part in the electrocardiographic changes.

Summary

Serial ECG's and serum enzyme estimations were performed on twenty patients with primary subarachnoid hemorrhage and abnormalities in these have been correlated with consci us state and arterial pCO levels. M jor changes in the ECG are not as f equent as in other reported series. The presence or absence of pathological Q waves is the most useful point in differentiation fr m myocardial infarction. Serum enzyme levels are elevated in both subarachn id hemorrhage and myocardial nfarction but consideration of the time pattern of enzyme elevation may be helpful n differentiation. The cause of the elect ocardiographic changes is unknown but a theory is advanced to explain these changes and to explain in part the associated enzyme abnormalities.

W wish t thank the physicians of The Royal Melbourne Hospital for permission to study their patients, Dr T K. Wong for help collecting the data, and M Roy Inglis for the preparation of the illustrations.

REFERENCES

1 Byer E., Ashman, R. nd Toth L. A Electrocardiogram with large upright T w ves and long Q-T interval, Am Heart J 33 796, 1947
2. Levine, H D Nonspecificity of the electrocardiogram associated with coronary heart disease, Am J Med 15:344 1953
3 Cropp G J and Manning G W Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial haemorrhage Circulation 22:25 1960
4 Hersch C. Electrocardiographic changes in subarachnoid haemorrhage, mening tis, and intracranial space-occupying lesions, Brit. Heart J 26 785 1964.
5. Koskelo, P Punsar S., and Sipila, W Subendocardial haemorrhage nd ECG changes in intracranial bleeding, Brit. M J 1 1479 1964.
6. Khein, M Schwarzschild, M M and Katz, H A nomogram for rate correction of the QT interval in the electrocardiogram, Am Heart J 35:990, 1948.
7 Locksley H B. Report on the co-operative study of intracranial aneurysms and subarachnoid haemorrhage. Section V Part I. Natural history of subarachnoid haemorrhage, i tracranial aneurysms and arteriovenous malformations, J Neurosurg 25:219 1966
8 Wasserman, F Choquette G., Cassinelli, R and Bellet S. Electrocardiographic observations in patients with cerebrovascular accidents, Am J Med. Sc. 231:502, 1956.
9 Shuster S. The electrocardiogram in subarachnoid haemorrhage Brit. Heart J 22:316, 1960
10. Burch G E., Meyers, R., and Abildskov, J. A. A new electrocardiographic pattern observed in cerebrovascular accidents, Circulation 9 719 1954
11 Hersch C.: Electrocardiographic changes in head injuries, Circulation 23:853, 1961.
12. Lipman, B S., nd Massie, E. Clinical scalar electrocardiography ed. 5, Chicago, Year Book Medical Publishers, Inc., 1965, p 259
13 Byer E., Toth L and Ashman, R. The electrocardiographic changes induced by cooling or warming the inner surface of dog ventricle, Am. J Physiol. 119:264 1937
14 Manning C W Hall, G. E and Banting, F G Vagus stimulation and the production of myocardial damage Canad. M A. J 37:314, 1937
15. Calvert, J M Premonitory symptoms and signs of subarachnoid haemorrhage, M J. Australia 1:651 1966.
16. Porter R. W Kamikawa, K., and Greenhoot, J H Persistent electrocardiographic abnormalities experimentally induced by stimulation of the brain, Am Heart J 64:815, 1962.
17 Yanowitz, F Preston, J B., and Abildskov J A. Functional distribution of right and left stellate innervation t the ventricles, Circulation Res. 18:416 1966.
18. Barger A. C., Liebowitz, M R., and Herd, J A. Chronic catheterization of the coronary artery infusion of utonomic drugs in the unanesthetized dog Fed. Proc. 20 101 1961.
19 Melville, K. I Blum, B., Shister H. E and Silver M D Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation, Am. J Cardiol. 12 781 1963.
20. Harrison, M T and Gibb, B H Electrocardiographic changes associated with a cerebrovascular accident, Lancet 2:429, 1964
21. Srivasta, S. C., nd Robson, A. O., Electrocardiographic abnormalities associated with subarachnoid haemorrhage, Lancet 2:431, 1964
22. Dubo, M Park D C., Pennington, R. J T Kalbag, R. M nd Walton, J N.: Serum creatine-kinase in cases of stroke, head injury or meningitis, Lancet 2 743, 1967
23 Connor R. C. R. Creatine kinase in intracranial lesions, Lancet 2:991 1967

Experimental and laboratory reports

Comparative evaluation of some DC cardiac defibrillators

R. C. Balagot, M.D.
J. R. Bandelin, M.D.
Chicago, Ill.

Conversion of ventricular fibrillation and certain other types of cardiac arrhythmias with an electronic defibrillator has become an accepted therapeutic procedure. The superiority of direct current (DC) over alternating current (AC) defibrillation has become established. Because of this, and the rush of many electronic companies to take advantage of a virtually untapped market, there has been a proliferation of available DC defibrillators. The universal criterion which influences the decision to procure a particular defibrillator is effectiveness based on theoretical considerations, e.g., energy output, or a limited clinical or experimental animal evaluation. A probable deficiency in rudimentary electronic knowledge detracts from the purchaser's ability to evaluate these instruments critically. It has become apparent that many of the factors involved in the clinical application of different types of DC defibrillators are not readily appreciated by the usual operator. An attempt is made in this report to demonstrate how these factors may differ or vary in a few representative and commercially available DC defibrillators.

This study compares the electrical characteristics of some available defibrillators in the hospital with respect to the following variables: (1) the energy delivered across the electrodes as a function of the selected energy setting in watt-seconds; (2) the variation of energy delivered as a function of the load or body resistance; (3) a comparison of energy stored in the capacitors against energy delivered; (4) a comparison of energy setting versus peak current for different body loads; and (5) a comparison of energy selected against peak voltage for various body loads.

Methods

There were two classes of DC defibrillators studied.

Class I was typified by the single inductance (L) capacitance (C) discharge circuit. The voltage and current discharge characteristics (waveforms) shown in Fig. 1 (A, B, and C) were typical for the single LC discharge circuit. The current and voltage varied in time coincidence, indicating that body loads which were resistive would also have had the current and voltage in phase. A difference in pulse widths existed among the single LC types made by different manufacturers. Representatives of this type tested were Model 10770 of the American Optical Company

From the Department of Anesthesiology, Presbyterian-St. Luke's Hospital, Chicago, Ill.
This study was supported by the Surgical Research Fund of the Division of Surgery at Presbyterian-St. Luke's Hospital, Chicago, Ill.
Received for publication July 1, 1968.

Vol. 77, No. 4, pp. 489-497, April, 1969

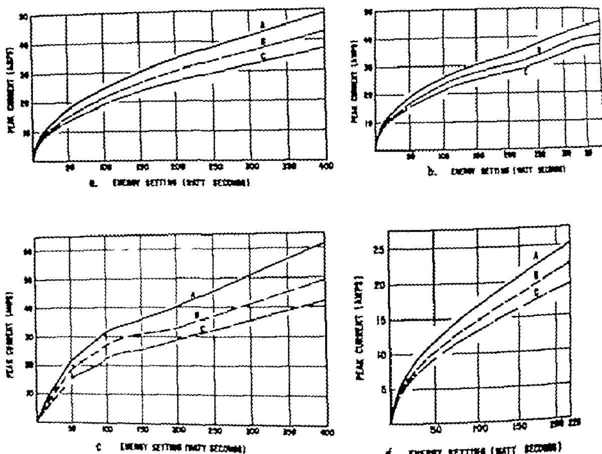


Fig 1 A B and C Characteristic waveforms of single inductance (L) capacitance (C) discharge circuit. These also show voltage outputs against (*A*) 100 ohm, (*B*) 50 ohm loads at 200 watt-second setting of defibrillator meter *D* Characteristic waveform of delay line discharge circuit also the voltage output against (*A*) 100 ohm (*B*) 50 ohm loads at 200 watt-second setting of defibrillator meter

referred to as Defibrillator I Model DSCK of the Corbin Farnsworth Company referred to as Defibrillator II and Model C 100-M of the Electrodyne Corporation Defibrillator III Defibrillator II differed somewhat from the usual LC type. Its condenser discharged into an iron-core transformer which stepped up the voltage. Nevertheless, its waveform remained essentially similar to the typical LC form Fig 1 *B* and was underdamped

The single LC discharge circuit is characterized by one of three responses when $(R/2L)^2 > 1/LC$, the circuit is overdamped or aperiodic when $(R/2L)^2 = 1/LC$ the circuit is critically damped when $(R/2L)^2 < 1/LC$ the circuit is underdamped or oscillatory R is the total circuit resistance.

Class II was of the delay-line discharge type Essentially it had two sections of capacitance (C) and inductance (L) and a characteristic impedance $R_o = \sqrt{L/C}$. The voltage and current discharge characteristics, i.e. the waveforms, are shown in Fig 1 *D* The pulse width is greater as compared to the single LC discharge circuit and has two characteristic bumps at the peak. The minimal dip between the bumps was achieved by a given value of mutual inductance between the two inductances The current and voltage are also in phase The representative member of this class tested was the Monopulse 807B referred to as Defibrillator IV marketed by Travenol Laboratories, Inc. but manufactured by Zenith Radio Corporation.

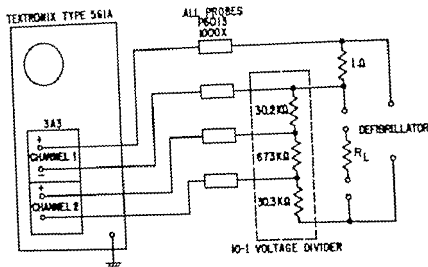


Fig 2 Schematic diagram of test apparatus. R_L adjustable to 50 ohms, 75 ohms and 100 ohms.

Methods and equipment

Transthoracic resistance of patients depended upon among other factors, their physical size, muscularity obesity and state of hydration. Three simulated values of thoracic resistance of 100 ohms, 75 ohms, and 50 ohms were used to provide a comparison of energy delivered to various chest sizes and types. A load resistance of 75 ohms was considered nominal transthoracic resistance.

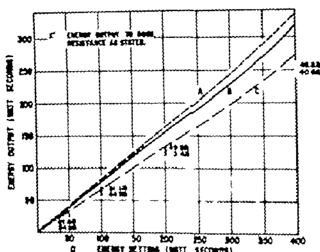
A Measurement of delivered defibrillator energy across a dummy load The energy delivered to a load at a given energy setting on the defibrillator under test was determined in the following manner (1) The voltage across the load and the current through the load as a function of time were measured simultaneously (2) these voltage and current waveforms were multiplied to obtain the power versus time curve (3) the area under the power versus time curve was measured with a planimeter The resulting area was then multiplied by the appropriate constant to give the energy delivered since $W = \int^{\infty} e(t)i(t)dt$.

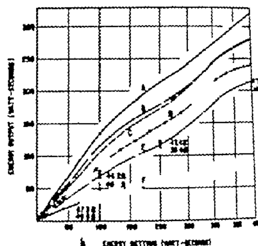
The system used to measure the voltage across the load and the current through the load is shown in Fig 2 A one ohm resistor was placed in series with the load and a high impedance 10 1 voltage divider was placed across the load. The voltage across the load and across the one ohm resistor was then measured using high voltage probes and differential amplifiers

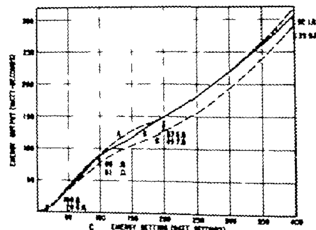
The voltage across the one ohm resistor provided a measure of the current through the load. The 10 1 voltage divider was placed across the load to furnish a constant finite impedance to 60 cycle stray fields regardless of the load impedance Without the divider it would be impossible to establish a base line in the clinical situation due to 60 cycle pickup inasmuch as the impedance seen by the stray fields was essentially infinite until the defibrillator was discharged into the dog thereby creating a low impedance load The P6013 voltage probes were necessary since the peak output voltage of some of the defibrillators that were tested exceeded 4 000 volts across a 100 ohm load

Differential amplifiers were used to keep the measuring system floating at all times single-ended measurements would have required grounding of one side of the load

The oscilloscope employed in this study was a Tektronix Type 561A fitted with a dual trace differential preamplifier (Type 3A3) The output voltage and current waveforms were photographed with a Polaroid camera. With this equipment calibration accuracy stability and dif







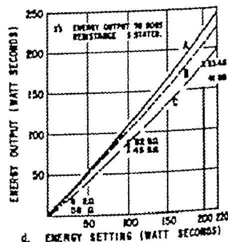


Fig. 3 nd d Energy output of Defibrillator I, III nd IV for (*A*) 100 ohm load, (*B*) 75 ohm load, and (*C*) 50 ohm load. X tand for dog trans-thoracic load. Fig. 3 b Defibrillator II—energy output for:

	Load ohm	*Line voltage*	*Discharge*
A	100	130	Delayed
B	100	115	Delayed
C	75	115	Delayed
D	50	115	Delayed
E	50	105	Delayed
F	50	105	Immediat
X	tated	115	Delayed

ferential balance were most important for accurate results. After a 24 hour warmup of the measuring equipment the differential balance of the preamplifier was adjusted with the probes disconnected from the preamplifier. Separate sets of internal balance controls were used for adjusting the differential balance depending upon the volts per division setting indicated on the front panel. After the nternal differential balance was made the probes were reconnected to the preamplifier and the differential balance adjusted using the controls located on the probe chassis. Finally adjustment of the gain of each channel was accomplished using the internal preamplifier gain controls and a 1 per cent voltage standard.

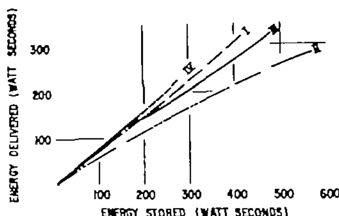


Fig 4 Energy delivered to 75 ohm load as function of energy stored for Defibrillators I II III and IV

The importance of these adjustments was crucial, since an error of 2 per cent in each channel could have resulted in an error of approximately 4 per cent in the power curve and, therefore in the output energy

POWER CURVE. The instantaneous amplitudes of voltage and current were measured on the photographs by means of a vernier caliper calibrated in thousandths of an inch The values of instantaneous voltage and current amplitudes were then multiplied to obtain the *power curve* The power versus time curve was plotted By measuring the areas under this curve with a planimeter the energy delivered was obtained.

The absolute accuracy of any valve of delivered energy determined by this method was estimated to be $\pm$ 5 per cent. This estimate included errors due to calibration, scaling plotting and planimetry

B Measurement of delivered energy across experimental animals Using the same methods described in Section A, four dogs around 20 and 12 kilograms in weight were substituted for the dummy loads. The dogs were under Nembutal anesthesia. Two 4 by 4 gauze pads were sutured to the chest wall immediately below the axilla at the level of the midaxillary line on both sides of the shaved chest. These were continually saturated with normal saline and served as constant sites for electrode application. Moderate pressure was exerted on the defibrillator electrodes compressing the chest somewhat before discharge of defibrillator energy across the dog thorax. Lead II of the dog ECG was monitored on another oscilloscope to demonstrate ventricular fibrillation or arrhythmias. The ECG scope was battery operated and isolated from the ground

Comparative traces were obtained with a 50 ohm dummy load and a 53 4 ohm transthoracic resistance of a dog The current and voltage waveforms were in phase (time coincidence) for both tracings, confirming that inductive and capacitive effects associated with body impedance were negligible at current densities of this magnitude. The single inductance-capacitor (LC) defibrillators also produced tracings which were identical for dummy and body loads.

Results

Energy output as a function of defibrillator output setting Sutton and associates have called attention to the importance of differentiating between delivered' energy and capacitor stored energy when determining energy thresholds for defibrillation It obviously becomes important, therefore, to compare energy control setting on the equipment with energy output.

Defibrillator I is equipped with a meter calibrated in watt-seconds, and depicted selected energy output. Fig 3 *A* is a plot of the energy setting in watt-seconds

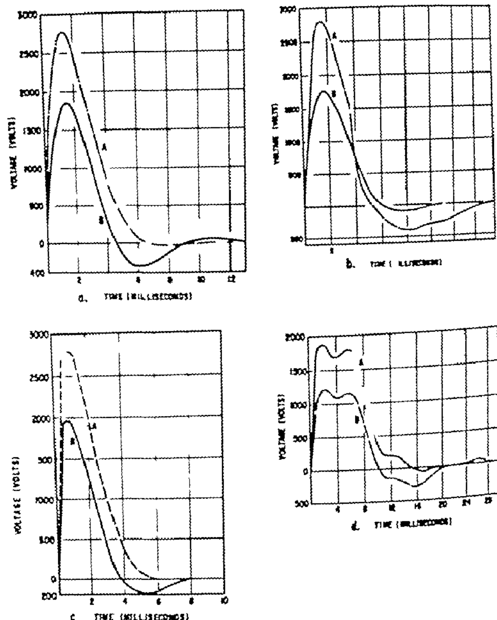


Fig 5 A B C and D Peak currents delivered by Defibrillator I II III and IV respectively ((A) 50 ohm, (B) 75 ohm, and (C) 100 ohm loads.

versus the energy output in watt-seconds delivered to resistance loads of 100 75 and 50 ohms and also to two dogs through the external defibrillation paddles For a maximum energy level of 400 watt-seconds and a nominal resistance of 75 ohms, the maximum delivered energy was 320 watt seconds. With an energy setting of 200 watt-seconds the energy delivered to a dog with a transthoracic resistance of 49 5 ohms was 130 watt-seconds

Defibrillator II used a multiposition switch for selecting the energy output setting and a ready light to indicate when the internal capacitors were charged and ready for discharge The charging voltage and the sensing circuit for the ready light were dependent on the power line voltage as determined by measurement of sensing threshold and charging supply Measurements showed that the charging circuit continued to charge for approximately

ten seconds after the ready light came on. Curves *A* through *E* in Fig. 3, *B* were obtained by discharging the defibrillator at least ten seconds after the ready light came on. In view of variations in commercial line voltage, a "worst" case study was made by adjusting the line voltage to 105 volts and discharging the defibrillator immediately after the ready light came on (Curve *F*). For a nominal resistance of 75 ohms and a nominal line voltage of 115 volts, the maximum energy output at the 400 watt setting was 280 watt-seconds (Curve *C*). For the "worst" case condition, a 400 watt-second setting resulted in delivery of only 87 watt-seconds, and an energy setting of 150 watt-seconds delivered 50 watt-seconds. Hunnicutt[3] reported almost identical results, in comparing outputs from Defibrillator I and Defibrillator II. Although load resistance was not specified in his publication, the values given suggest that a 75 ohm resistance was utilized.

Defibrillator III also employed a meter to indicate the energy level of the defibrillator setting controlled by an output knob. Fig. 3, *C* shows the energy output as a function of the energy setting on the meter. For a nominal 75 ohm load, a 400 watt-second setting delivered 320 watt-seconds output and at 200 watt-seconds, it discharged 150 watt-seconds.

Defibrillator IV was of the delay-line discharge type with an energy setting indicated on a meter calibrated in watt-seconds. The energy level was selected by means of a control knob. Fig. 3, *D* shows the output energy as a function of energy setting for a nominal resistance of 75 ohms at 200 watt-second setting, approximately 200 watt-seconds were delivered. The maximum setting of this instrument was 220 watt-seconds and 220 watt-seconds were delivered to a 75 ohm load.

Stored versus delivered energy. To depict the energy stored by the four equipments studied, Fig. 4 was prepared and was a composite of the measured energy delivered to a 75 ohm load as a function of the energy stored. The energy stored was calculated from the relation: Energy stored $= \frac{1}{2}CV^2$ where C was the capacitance of the storage capacitor(s) in the defibrillator expressed in farads and V was the voltage to which the capacitor(s) was charged. By comparing the stored energy to the delivered energy, an estimate was made of the efficiency of the instrument. The terminus of each curve represents the maximal stored energy for each defibrillator. As shown in this plot, Defibrillator I was apparently calibrated in stored energy; at the maximal setting of 400 watt-seconds, 400 watt-seconds of energy were stored and 320 watt-seconds were delivered to a 75 ohm load corresponding to Curve *B* of Fig. 3, *A*. It was apparent that Defibrillators II and III were not calibrated in either energy stored or energy delivered to the load (Curve *C*, Fig. 3, *B*, and Curve *A*, Fig. 3, *C*, respectively). Defibrillator IV was calibrated in delivered energy against a 75 ohm load, Curve *B*, Fig. 3, *D*.

Peak current delivered as a function of energy setting. In Fig. 5, *A*, *B*, *C*, and *D*, peak current delivered to several loads as a function of the energy setting of the various defibrillators is plotted. At 400 watt-seconds, single LC defibrillators delivered currents of 45 to 60 amperes into 50 ohm body loads. Peleska[4] and others[5,6] have shown currents of this magnitude to cause arrhythmias. At 200 watt-seconds, the delay line type defibrillator delivered a peak current of approximately 22 amperes to a 75 ohm load as compared to 30 to 33 amperes for the single LC type defibrillators (Fig. 5, *D*).

Output voltage as a function of load resistance. Fig. 1, *A*, *B*, *C*, and *D* shows the waveforms as a function of the load resistance. Two of the single LC type defibrillators were critically damped for loads of 100 ohms, but were somewhat underdamped for loads of 50 ohms. Peak voltages with a 200 watt-second setting were approximately 2,800 volts for a 100 ohm load. Fig. 1, *B* illustrates the considerable distortion in the voltage waveform of this defibrillator against 100 ohms as compared with that against 50 ohms. This may have resulted from the electrolytic capacitor discharge hysteresis and core characteristic of the output transformer. Fig. 1, *D* shows that the waveform was essentially undistorted for different loads in the delay-line type defibrillator. The output voltage was in the neighborhood of 1,800 volts for 200

watt-second setting and 100 ohm load. The delay line voltage output was about two thirds as large as those for the single LC section defibrillators.

Discussion

The sole criterion employed by most users of DC defibrillators is effectiveness in converting a ventricular fibrillation or in selected instances conversion of an arrhythmia. Seeming innocuousness of the brief energy pulse delivered by these units has established an equal and similar image for all these defibrillators. Infrequency of observation of deleterious effects has tended to obscure the possibility of their occurrence. Nevertheless these effects do occur, e.g., the possibility of ventricular fibrillation in the nonfibrillating heart (application of the defibrillator without benefit of ECG) in a suspected cardiac arrest. The existence of potential pathways for energy losses emphasizes this possibility even more. Peleska has shown that trauma to the myocardium is directly related to the voltage magnitude. Dętmer and associates have made similar observations and demonstrated relative safety of LC waveforms with lower voltages but equivalent energies. Apparently once a voltage peak was reached that was sufficient to force an energy pulse through the chest and depolarize the heart, additional voltage was unnecessary and hazardous. Excessive current may provoke ionization in the myocardial cell, possibly in the alveolar cell or the cell membrane, and cause subtle changes of unappreciable significance. For instance, in a previous study, repeated fibrillation-defibrillation sequences performed on dogs showed a progressive and significant decrease in arterial pO_2 despite adequate ventilation, which might signify alveolar cell or membrane damage, and thus inadequate alveolar O_2 absorption.

The voltage and current delivered by an LC circuit depends on the resistance between electrodes. Knowledge of this parameter is essential for optimal defibrillation, yet it is a virtual impossibility at present to obtain this value for every patient just before defibrillation. Thus some average value of resistance against which all LC defibrillators may be calibrated for delivered energy is desirable. The thoracic resistance encountered in the average adult patient is around 75 ohms, when the energy is delivered via electrodes of the usual diameters employed by most manufacturers (8 to 9 cm.). The calibration of the energy (watt-second) meter to read *delivered energy* across this resistance would seem to be logical and preferable to reading either stored or theoretically stored energy. The lack of any standard method for regulating the energy output of commercially available defibrillators in relation to some average resistance diminishes greatly and perhaps dangerously the operator's control over this energy. Our study has demonstrated the wide differences of voltage and current among four defibrillators made by different manufacturers. The variation in delivered energy as compared to the selected energy level on the meter is great. As illustrated in Fig. 3, the outputs of the three single LC defibrillators ranged from 20 to 78 per cent below the energy selected by the operator. Based on this discrepancy between selected and delivered energy, it is not at all improbable that a low energy pulse may be delivered to a normal heart and induce fibrillation.

Fig. 4, which compares the four defibrillators tested with respect to the actual energy delivered as opposed to stored energy, again accentuated what amounted to almost a haphazard manner in which some of these emergency therapeutic electronic units were prepared. Defibrillator I, for example, was calibrated in stored energy, but Defibrillators II and III were neither calibrated in stored nor delivered energy, and despite the known dependence of delivered voltage and current of an LC circuit to resistance, none of the three showed concern for this important and vital relationship. Some of the dangers associated with these inconsistencies in the manufacture of these products have been pointed out. The watt-second meter of Defibrillator IV was calibrated to express delivered energy to a 75 ohm resistance.

Fig. 1 illustrates a very interesting characteristic of both the LC circuit and the delay line circuit, i.e., with increasing load or resistance, the energy delivered increased, and with a smaller resistance the

amount of delivered energy also decreased. This apparently was due to internal loss of energy which diminished as resistance encountered increased (increased efficiency with increased resistance) and increased as resistance diminished (decreased efficiency).

Summary and conclusions

1. Four commercially available defibrillators were subjected to extensive tests of electrical characteristics.

2. Three of the defibrillators evaluated were found to deliver substantially less energy (20 per cent to 8 per cent less) than indicated by the energy selector controls, when discharged to a range of resistance usually encountered clinically.

3. The energy delivered by all LC circuit defibrillators varied as a function of body resistance. Unless calibrated in *delivered energy* rather than stored energy, the output may vary widely among defibrillators of different manufacturers.

4. All units tested had a characteristic internal loss of energy which was superimposed on the loss due to mismatch with body resistance.

5. The single LC defibrillators, with waveforms of three or four milliseconds in duration achieved extreme peak voltage and current amplitudes at high energy level selection. These amplitudes had previously been shown to be deleterious.

6. Since resistance measurements are generally not available to the clinician and conversion tables relating stored energy to delivered energy would be awkward at best, some standardization of the outputs of defibrillators is indicated. It is suggested that calibration of the energy setting to indicate *delivered energy* to a 75 ohm load be adopted generally.

REFERENCES

1. Kouwenhoven, W. G., Milnor, W. R., Knickerbocker, G. G., and Chesnut, W. R.: Closed chest defibrillation of the heart, Surgery 42:550, 1957.
2. Sattor, W. A., Galysh, F. T., and Hagan, W. K.: Determinants of DC defibrillation success, Clin. Res. 15:224, 1967.
3. Hunnicutt, M. S.: Safety considerations in the use of DC defibrillators, Am. Optical Co., 1964.
4. Peleska, B.: Cardiac arrhythmias following condenser discharges and their dependence upon strength of current and phase of cardiac cycle, Circulation Res. 13:21, 1963.
5. Peleska, B.: Cardiac arrhythmias following condenser discharges led through an inductance, Circulation 16:11, 1965.
6. Balagot, R. C., Druz, W. S., Ramadan, M., Lopez Bello, M., Jobgen, E., Tomita, M., and Sadove, M. S.: A monopulse DC current defibrillator for ventricular defibrillation, J. Thoracic & Cardiovas. Surg. 47:487, 1964.
7. Balagot, R. C., Gordon, A. S., Druz, W. S., Jobgen, E., and Sadove, M. S.: What is DC cardiac defibrillation, Scientific Exhibit of the A. M. A., San Francisco, 1964.
8. Stoeckle, H., Nellis, S. H., and Schuder, J. C.: Incidence of arrhythmias following experimental ventricular defibrillation, Proc. of the Annual Conference on Engineering in Med. and Biol. Vol. 9, 1967.
9. Dettmer, R. A., Rausch, J., Fletcher, E., and Gordon, A. S.: Ideal waveform and characteristics for direct current defibrillators, Fiftieth Annual Clin. Congress, Am. College of Surgeons, Forum 15:249, 1964.

Effect of hypoxia on the vascular response to isoproterenol and norepinephrine*

Thomas T. Zsoldr, M.D., F.R.C.P.(C), F.A.C.P.
Toronto, Ontario, Canada

The effect of acute or chronic hypoxia on the cardiovascular system has been extensively investigated. The influence of both the arterial and anemic hypoxia on cardiac function and on the arterial resistance in various tissues has received a great deal of attention. In contrast, almost no data have been found on whether hypoxia would modify the effect of vasoactive drugs on the vessels. It was felt that hypoxia may interfere with the normal vasoconstric or and dilator effect of drugs by at least two distinct mechanisms. First, the oxidative metabolism of vascular smooth muscle could be depressed and this could interfere with constriction and dilation. Second, hypoxia may affect the action of certain drugs on the receptors in the vessels.

Consequently, it was decided to study whether acute arterial hypoxia would have a modifying effect on the response of the peripheral circulation to various vasoactive drugs. This paper deals with experiments in animals related to two widely used drugs, isoproterenol and norepinephrine. It would also be of interest to learn from this study whether hypoxia would alter the response of arteries and veins in a similar or dissimilar manner.

Methods

Mongrel dogs weighing 15.0 to 28.0 kilograms were anesthetized with sodium pentobarbital, 30 mg. per kilogram, were given intravenously, followed by maintenance doses as required. Heparin (Connaught Laboratories), in a dosage of 300 USP units per kilogram given intravenously, was used as anticoagulant. A tube was inserted into the trachea of the animals, but respiration was not assisted.

The femoral artery was cannulated and perfused with blood from the right atrium, through a Bardick cannula introduced via the jugular vein, at a constant flow rate. A Sigmamotor pump was used for perfusing the hind limb at a pressure close to the initial pressure measured in the femoral artery prior to cannulation. This flow rate was then maintained throughout the whole experiment unless specified otherwise in the

Results. Pemco micro disc oxygenator Model 7104 was inserted into the system (as shown in Fig. 1) between tubes leading to the jugular vein and to the Sigmamotor, respectively. Oxygen level of the blood perfusing the femoral artery was altered by changing the speed of the disc rotation. In the first part of this study, a tank contain-

With the technical assistance of Camille Wolchuk, B.Sc.
From the Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada.
Supported by the Ontario Heart Foundation.
Received for publication July 1, 1968.
*Partly presented at the meeting of the Canadian Federation of Biological Societies, Kingston, Ontario, June, 1968.

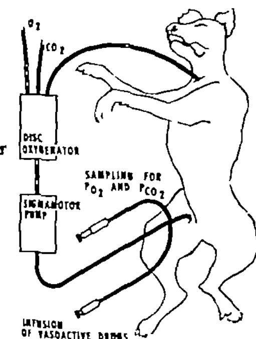


Fig. 1. Experimental arrangement. Catheters in the jugular vein and the femoral artery. Blood oxygenated with disc oxygenator. Constant flow perfusion with Sigmamotor pump.

ing a mixture of 95 per cent O and 5 per cent CO_2, and in the second part two tanks, one containing 100 per cent O and the other 100 per cent CO_2, were connected to the oxygenator. The flow rate of 95 per cent O plus 5 per cent CO or of 100 per cent O from the tank was kept constant, while that of 100 per cent CO was much lower and adjusted to produce CO levels between 35 and 40 mm. Hg in the perfused blood. For analysis of P_{O_2} and P_{CO_2}, blood was sampled from the tube leading to the femoral artery from the Sigmamotor pump. P_{O_2} and P_{CO_2} were measured in the blood immediately after collection with a Beckman Model 160 gasanalyzer. Three different oxygen levels were used for perfusing the femoral artery: (1) low oxygen tension, i.e., blood from the right atrium; (2) moderate oxygen tension, P_{O_2} between 60 and 90 mm. Hg; and (3) high oxygen tension, P more than 100 mm. Hg.

Following perfusion of the hind limb with blood of a given oxygen level for at least 30 min., in one group of dogs norepinephrine was infused into the femoral artery and in the other group isoproterenol was infused into the femoral artery. The experiments started with the perfusion of blood of low or high oxygen tension alternately. The drugs were given with a Harvard infusion pump, Model 903, at a rate of 1 c.c. per minute, through the tube leading to the femoral artery. Norepinephrine bitartrate (Levophed, Winthrop Laboratories) and isoproterenol hydrochloride (Winthrop Laboratories) were used, diluted with saline. Both catecholamines were infused in gradually increasing doses of 0.3, 1.0, and 3.0 μg of base per minute, each dose for 5 minutes, i.e., for a total of 15 minutes.

Pressures were simultaneously recorded in the femoral artery and vein, in the small vein of the paw, and in the small vein of the quadriceps muscle of the perfused hind limb, systemic pressure above the cannulation of the femoral artery was recorded. Polyethylene tubes, which measured 0.05 inch around the outside diameter, were introduced from a side branch into the femoral artery or vein and directly into the small veins as in our previous experiments.[1] Pressures were recorded by a Statham P 23 AC transducer on a Grass Model 7 Recorder with a 0.5 mm. per second paper speed during the whole experiment.

Vascular resistance was calculated in resistance units (RU) as pressure gradient (mm. Hg) divided by blood flow (milliliter per minute). Pressure difference between artery and small vein was used for calculation of arterial resistance, while pressure difference between small and large veins was used for calculation of small vein resistance; for calculation of resistance in large veins, pressure was divided by flow values.

Results

Pressure in the femoral artery prior to cannulation in 26 dogs was 151.1 ± 3.0 *mm.* Hg (mean ± S.E.); 13.1 ± 1.3 mm. Hg in the small vein of paw; 13.4 ± 1.3 mm. Hg in muscular small vein; and 3.7 ± 0.4 *mm.* Hg in femoral vein. The mean perfusion flow required to maintain arterial pressure near this level was 76.1 ± 5.4 ml. per minute. Oxygen tension in the femoral artery was 80.9 ± 4.8 mm. Hg in the few dogs

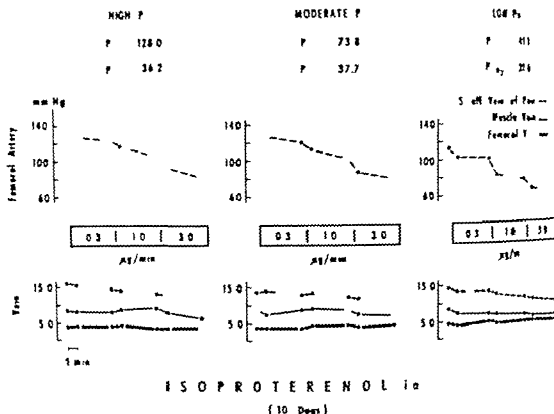


Fig. 2. Pressure in the femoral artery and in the veins in 10 dogs during infusion of isoproterenol into the artery. Mean O and CO₂ tension of perfusing blood before the drug was given are shown.

where pH was measured it varied between 7.37 to 7.41.

Pressure in the femoral artery was lower during perfusion with nonoxygenated blood of low oxygen tension than during perfusion with blood of high ($P_{O_2} > 100$ mm Hg) or moderate oxygen tension (P_{O_2} 60 to 90 mm Hg). This can be seen in Figs. 2 and 4 where the control values prior to drug administration represent pressures measured following a period of perfusion lasting at least 30 min with blood of different oxygen content. The mean of arterial pressure in 26 dogs was 143 mm Hg when venous blood was perfusing the hind limb; there was no significant difference between the first two values but both were significantly higher than the third ($p < 0.01$) using the t test for paired samples. It was interesting to find that pressures in the small and large veins remained virtually the same while perfused with blood of various oxygen tension.

The infusion of isoproterenol into the femoral artery in gradually increasing doses resulted in consistently decreased pressure in the artery and decreased pressure to a lesser extent in the small veins. While control pressure in the femoral artery was different depending on blood used for perfusion of the limb, the vasodilation was of the same proportion as shown on Fig. 2. Systemic pressure, measured above the cannulation of the femoral artery, was unaltered during the intra-arterial administration of the 0.3 and 1 μg per minute dose of isoproterenol while some decrease was usually seen at the end of the infusion of the 3 μg per minute dose. Mean pressure decrements and standard errors in the perfused artery and small vein of paw are given in Fig. 3. These values were obviously similar regardless of the oxygen tension of the perfusing blood. As flow in the hind limb was constant in our experiments, the pressures were representative of vascu

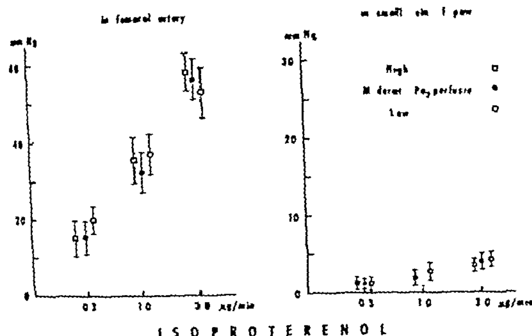


Fig. 3. Mean ± standard error of pressure decrements in 10 dogs. Pressure changes in fifth minute of infusion of isoproterenol into the femoral artery are represented.

lar resistance. Isoproterenol decreased resistance in the artery and small vein of paw in the same proportion whether blood of high, moderate, or low oxygen tension was perfusing the leg (Table I).

Intra-arterial infusion of *norepinephrine* consistently increased pressure in the femoral artery, and higher doses (1 and 3 µg per minute) consistently increased pressure in the small veins also, while pressure in the femoral vein was not affected. Figs. 4 and 5 demonstrate that the pressure increments in the artery were similar when blood of high or low oxygen tension was perfusing the hind limb. In contrast, during perfusion with partially oxygenated blood (P_{O_2} 60 to 90 mm. Hg), pressure response in the femoral artery to the dose of 1 and 3 µg per minute norepinephrine became significantly less ($p < 0.05$) than in other experiments, although the initial pressure was similar. This diminution of the effect of norepinephrine was not evident in the small veins during perfusion with hypoxic blood. When vascular resistance was calculated separately for arteries and for the small and large veins, and increments produced by norepinephrine were compared at various perfusions, significantly less effect ($p < 0.05$) was observed in the arteries during perfusion with blood of moderate oxygen tension (Table I). Systemic pressure was not affected by intra-arterial norepinephrine in the doses used in these experiments, and therefore pressure or resistance changes observed reflect the local action of the drug.

While perfusion rate described in the above experiments was kept constant, in 6 additional dogs perfusion with venous blood was combined with *diminution of perfusion pressure*. In 3 dogs norepinephrine was infused into the femoral artery, and in 3 other dogs isoproterenol was infused into the femoral artery in the above doses. First, and at the end of the experi-

Table I. Vascular resistance. Fifth minute values during 3 μg/min. infusion compared to control value

Drug (3 μg/min intra-arterial)	No. of dogs	P_{O_2} of perfusing blood	Alteration in % of control values		
			Femoral artery	Small vein of paw	Femoral vein
Isoproterenol	10	128.0	−42.1	−47.0	0
		73.8	−41.8	−50.0	−2.1
		41.1	−42.6	−47.5	0
Norepinephrine	10	125.6	+20.2	+157.0	+6.5
		71.9	+ 3.5	+100.2	+5.4
		34.8	+22.8	+180.1	+7.7

ment the leg was perfused with oxygenated blood (P_{O_2} > 100 mm Hg) but in the middle of the experiment the leg was perfused with venous blood at about half of the control pressure i.e. at 60 mm Hg. At the lower perfusing pressure though total resistance in the artery was not diminished isoproterenol decreased pressure in the femoral artery and in the small vein of paw to a lesser degree. Fig 6 which is from a record of another dog shows pressure in the femoral artery which demonstrates that low oxygen tension of perfusing blood did not prevent isoproterenol effect but only when the perfusing pressure too was greatly diminished. The pressure increment produced by norepinephrine though less in absolute value was similar in percentage during perfusion with blood of high and low oxygen tension at a diminished flow rate.

Discussion

The essential variable in the above experiments was the oxygen tension of the perfusing blood. Some other factors varied too and will be considered in the evaluation of the results. Arterial as well as venous resistance was lower than in our previous experiments,[1] when intact circulation was studied and blood flow was measured with an electromagnetic flowmeter. The release of vasodilator substances from red blood cells during perfusion with Sigmamotor pump seems to us the proper explanation for this difference. Some hemolysis became evident at the end of the experiments. As the study was designed so that arterial and venous perfusion were the first in an equal number of dogs, the presence or absence of hemolysis could hardly account for the effect of various oxygen levels on drug response.

Heat loss through the oxygenator was unimportant. Probably not more than 5 per cent of cardiac output passed through to the oxygenator and blood temperature measured in several animals was only 1 degree C. lower after having passed the extracorporeal circulation (i.e. in the tube leading to the femoral artery).

CO_2 tension in the venous blood perfusing the limb was low. Loss of CO_2 while blood passed through the disc oxygenator was thought to be responsible for this. One cannot deny the possibility that lower CO_2 tension in venous blood compared to blood of moderate or high oxygen tension, would affect drug responses and therefore interfere with the effect of variation of oxygen tension. It seems rather unlikely however that a P_{CO_2} lower in the venous blood by only 5 mm Hg should seriously interfere with the effect of low P_{O_2} in our experiments.

Resistance in the femoral artery consistently decreased following perfusion with blood of low oxygen tension. This is to be expected from the well-known vasodilator effect of hypoxia. Oxygen tension above 60

HIGH P — P 125.6 — P $_{O_2}$ 35.3

MODERATE P — P 71.9 — P 36.9

LOW P — P 37.8 — P 31.5

Mal VEIN —
Femoral VEIN —

180 / 160 / 140

0.3 | 1.0 | 3.0 µg/m

30 / 10

NOREPINEPHRINE
(10 Dogs)

Fig. 4. Pressure in the femoral artery and in the veins in 10 dogs during infusion of norepinephrine into the artery. Mean P_{O_2} and P_{CO_2} of perfusing blood are shown.

PRESSURE INCREASE PRODUCED BY NOREPINEPHRINE

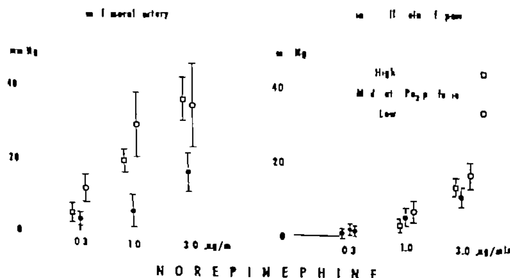


Fig. 5. Mean ± standard error of pressure increments in 10 dogs. Pressure changes during the fifth minute of infusion of norepinephrine into the femoral artery are represented.

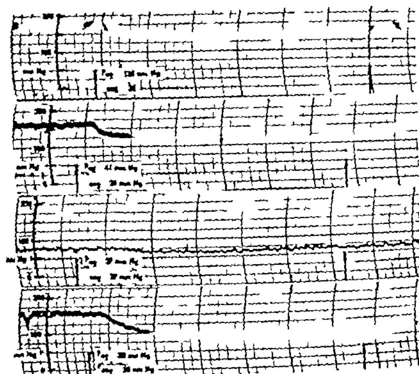


Fig 6 Fre si) l artery d ring five minute intra arterial infusion (1 μg per minute) of isoproterenol I the first rec d top the artery was perfused with arterial blood and in subsequent records the artery w perf sed w th enous blood Isoproterenol almost failed to dilate the vessel in the third test when perfusing pressure w din in shed

mm Hg was n t sufficiently low to produce vasod lation This ould suggest as has been observed by Daugherty and associates[7] that in the liml vessels of the dog Po_2 has to be d m n shed substantially to produce relaxation of the arteries In renal vessels resistance was reported to decrease with much less diminution of Po_2. Such a difference between vessels supplying various areas is conceivable and might be consequent to difference in the r nervous control The innervation of small vessels was left intact in our experiments and therefore they were under reflex regulation Nahas and associates[6] found that inhalation of 8 per cent oxygen in nitrogen increased pressure in small veins In our experiments pressure and resistance of small and large veins was not altered by perfusion with blood of low oxygen tension This is to be expected since the oxygen tension in the capacitance vessels is low even under normal circumstances.

Vasoconstriction produced by norepinephrine and vasodilation produced by isoproterenol were virtually unaffected by perfusion of the limb with blood of low oxygen tension. We have no proof that Po_2 in the vascular smooth muscle and at the drug receptors would become identical with that measured in the perfusing blood Fast equalization however seems likely and we allowed at least 30 min. for this before drugs were again administered. Recently Detar and Bohr[4] reported that epinephrine caused less constriction in the aortic strip of the rabbit when Po_2 was diminished to below 100 mm Hg In those experiments, the vessels are probably exposed to less oxygen than in our in vivo experiments using perfusion with a high flow rate. Cronin[8] found that nitroglycerin in coronary vessels of dogs perfused with hypoxic blood failed to decrease resistance any further Similarly in our experiments, when both the perfusing pressure and the Po_2

were diminished isoproterenol produced less vasodilation Norepinephrine was also effective under these conditions When the perfusing pressure was in normal range, we found that in the hind limb constriction and dilation of both the arteries and veins were apparently not affected by low oxygen tension This would suggest that very little oxygen is needed in the vessels for oxidative metabolism to cover the expenditure of constriction and dilation. This conclusion would fit with the observation of Howard and associates, who by measuring in vivo oxygen consumption of arteries and veins, found that P_{O_2} can be reduced to about 5 mm. Hg before the uptake of oxygen in the vessels would be diminished.

Our results indicate that during perfusion with moderate oxygen tension blood norepinephrine caused less vasoconstriction than during perfusion with blood of high or low oxygen tension. This strange phenomenon is difficult to explain. It might be related to an effect on the alpha-adrenergic receptors resulting in decreased binding or increased metabolism of norepinephrine, or both. Before speculating on the explanation of this interesting finding we would like to see whether other vasoactive drugs would have a similarly depressed response at moderate diminution of oxygen tension

Under various clinical conditions, such as shock and various forms of hypoxia etc. reduction of P_{O_2} is usually associated with hypercapnia and acidosis. The latter factors also have to be considered in the alteration of vascular response to norepinephrine or isoproterenol in light of the practical conclusions from the above experiments.

Summary

We studied whether hypoxia would alter vasoconstriction produced by norepinephrine and vasodilation produced by isoproterenol The hind limb of the dog was perfused at constant flow rate with blood of low oxygen tension which was altered by a disc oxygenator

Perfusion with blood of low oxygen tension decreased resistance in the artery but not in the small or large veins of the leg

Perfusion of the femoral artery with blood of low oxygen tension did not affect the response to intra-arterial norepinephrine or to isoproterenol. The results suggested that oxygen tension of the blood could be decreased to a considerable degree before vascular smooth muscle would fail to constrict or relax.

Norepinephrine caused significantly less constriction in the artery though not in the veins, when the perfusing blood was of moderate oxygen tension (P_{O_2} 60 to 90 mm. Hg) than during perfusion with blood of high (P_{O_2} more than 100 mm. Hg) or low oxygen tension.

REFERENCES

1 Zsotér T and Tom, H. Adrenoceptive sites in the veins Brit. J Pharmacol. 31:407 1967
2 Daugherty R M Scott, J B. Dabney J M and Haddy F J Local effects of O_2 and CO_2 on limb, renal, and coronary vascular resistances, Am. J Physiol. 13 1102 1967
3 Lockett, M F Effect of changes in P_{O_2}, P_{CO_2} and pH on the total vascular resistance of perfused cat kidneys, J Physiol. 193:671 1967
4 Nahas, G. G Josse, J W and Mather J C. Influence of acute hypoxia on peripheral and central venous pressures in non-narcotized dog, Am. J Physiol. 177:315 1954
5 Detar R and Bohr D F Oxygen and vascular smooth muscle contraction, Am. J Physiol. 214:241 1968.
6 Cronin, R. F P Influence of arterial oxygen tension on the coronary vasodilator action of nitroglycerin, Circulation 34 (Suppl. III):81 1966.
7 Howard R. O Richardson, D W Smith, M. H., and Patterson, J L. Oxygen consumption of arterioles and venules as studied in the Cartesian Diver Circulation Res. 16:187 1965.

Gross morphology and arterial supply of the papillary muscles of the left ventricle of man

N. Ranganathan, M.D.
G. E. Burch, M.D.
New Orleans, La.

The papillary muscles play an important role in the preservation of the competence of the atrioventricular valves. This has become more evident since the recent description of the clinical syndrome of papillary muscle dysfunction. The anatomists and the cardiologists have neglected the morphologic characteristics of the papillary muscles except to note that the papillary muscles are specialized forms of trabeculae carneae and that they are variable in number, size, and shape. Similarly, the vascular anatomy of this region of the ventricles has received little attention until recently. The following report describes the morphologic characteristics and vascular anatomy of the papillary muscles and the relationship between them based upon detailed post-mortem angiographic investigations including stereoradiography[4] and histologic examination. The method of stereoarteriography was employed because of its advantage over corrosion and clearing techniques. Stereoradiographs provide a clear display of the small coronary vessels as well as the morphologic myocardial background and permit histologic studies in any selected area of the myocardium.

Materials and methods

Ten hearts obtained from routine autopsies were studied. The right and left coronary arteries were cannulated while the specimen was still fresh and unfixed. The coronary vascular bed was flushed to eliminate obstructing clots. The cannulas, while still filled with saline, were connected under water by means of adapters and tubings to a reservoir containing the injection mass. The latter consisted of barium sulfate of a very small particulate size (Micropaque). About 200 to 300 ml. of a 20 per cent solution of Micropaque in 10 per cent formalin was injected at temperatures of 35 to 37° C. at a pressure of 100 to 120 mm. Hg for about 20 minutes, using a sphygmomanometer cuff with intermittent manual compression. This was followed by injection of about 50 to 100 ml. of 40 per cent Micropaque in 10 per cent gelatin. The gelatin was used to ensure adequate sealing when the heart was subsequently cooled. After the injections were completed, the heart was cooled to hasten the solidification of the injection mass. The heart was then divided by partial dissection into (1) atrial block and (2) ventricular block. No transventricular section or

From the Department of Medicine of the Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans, La.
Supported by grants from the United States Public Health Service, the Rowell A. Billups Fund for Research in Heart Disease, and the Rudolph Matas Fund for the Kate Prewitt Hess Laboratory.
Received for publication July 8, 1968.

apical section was made so as not to disturb the papillary muscles. The ventricular block was unrolled as described by Fulton. The heart was then examined carefully the morphologic characteristics of the papillary muscles were noted and the measurements were taken. Particular attention was paid to the shape of each papillary muscle, its size the number of component parts, its spatial orientation and attachments. However it was difficult to ascertain the spatial gross morphology of the papillary muscles until longitudinal sections were made through these muscles.

After the initial examination the ventricular and the atrial blocks were fixed in 10 per cent formalin for a period of at least 24 to 48 hours. Stereoscopic radiographs of these formalin-fixed blocks were then taken using x ray equipment (Model 6191 Picker Industrial apparatus) rated at 50 kilovolts and 10 milliamperes, and provided with a thin beryllium window The technique used was that reported for the cerebral circulation by Hale and Reed The x-rays were taken at 28 kilovolts and 7 milliamperes with exposure time ranging from 25 to 35 minutes. The stereoradiographs of the entire ventricular block, with both coronary arteries and all their ventricular branches intact, served as a reference for later sections. Two to three myocardial segments were sectioned from the left ventricle, each segment including one group of papillary muscles and the entire subjacent ventricular wall. Stereoscopic radiographs of these sections were also obtained. Longitudinal sections, 1 0 to 2.0 cm thick through each group of papillary muscles from base to apex were then made. When there was more than one belly for the respective papillary muscle sections were made for each. The sections were placed directly on a photomechanical film (3M Company Size No. 5) and exposed to x rays at 28 kilovolts and 7 milliamperes for a period of 5 to 12 minutes. These stereoscopic radiographs were then examined in detail for the vascular anatomy They served as a guide to histologic studies conducted on sections made not only from the region of the papillary muscles but also from adjacent portions of the free wall of the left ventricle Diameters of the vessels were determined by direct measurements from enlargements (11 times) of the radiographs.

Results

The diagnoses for the ten patients whose hearts were studied are noted in Table I Severe coronary atherosclerosis was present in the hearts of two patients, moderate coronary atherosclerosis was noted in two minimal atherosclerosis of the coronary arteries in five and normal coronary vasculature in one.

The morphology of the papillary muscles of the left ventricle The gross morphologic characteristics of the anterolateral and posteromedial papillary muscles of the left ventricles in the ten hearts studied are summarized in Table II In general, the papillary muscles were classified under

Table I Clinical and autopsy diagnoses for the 10 patients whose hearts were studied

Heart no.	Age	Race*	Sex	Diagnoses
1	77	N	M	Adenocarcinoma of the pancreas, minimal coronary atherosclerosis
2	51	N	M	Bronchogenic carcinoma, minimal coronary atherosclerosis
3	19	N	M	Penetrating wound of aorta, normal coronary vasculature
4	47	C	M	Cerebral hemorrhage, severe coronary atherosclerosis
5	60	C	M	Pneumococcal pneumonia, moderate coronary atherosclerosis
6	66	C	F	Massive pulmonary hemorrhage, minimal coronary atherosclerosis
7	66	C	M	Hepatoma, minimal coronary atherosclerosis
8	62	N	M	Subdural hematoma, severe coronary atherosclerosis
9	47	N	M	Accidental transection of the aorta, moderate coronary atherosclerosis
10	55	C	M	Pulmonary tuberculosis minimal coronary atherosclerosis

*N stands for Negro, C stands for Caucasian.

Table II Morphologic characteristics, arterial supply, and histopathology of the left ventricular papillary muscles of the 10 hearts

Heart no.	Anterolateral papillary muscle: Morphology	Anterolateral papillary muscle: Arterial vasculature	Anterolateral papillary muscle: Histopathology	Posteromedial papillary muscle: Morphology	Posteromedial papillary muscle: Arterial vasculature	Posteromedial papillary muscle: Histopathology
1	Fingerlike	Central artery	Central artery showed subintimal and some medial fibrosis. Focal fibrosis in the tip	[illegible]	[illegible] long [illegible] vessel	Normal
2	Tethered	Segmental distribution	Normal	Intermediate	Segmental distribution	Normal
3	Tethered	Segmental distribution	Normal	Intermediate with fingerlike portion	Central artery, some segmental distribution	Normal
4	Tethered	Severe atherosclerosis intramyocardial vessels thin narrow and few enlarged subendocardial vessels	Extensive fibrosis the subjacent ventricular wall; minimal fibrosis in the papillary muscle	Tethered		Enlarged subendocardial vessel
5	Intermediate base moved upward	Segmental distribution some intramyocardial vessels narrow and one occluded	Normal	Mainly fingerlike with two distinct bellies	Separate central artery to each belly	Normal
6	Intermediate; a free lateral belly	Segmental distribution central artery to lateral belly	Normal	Intermediate	Several long intramyocardial vessels	Normal
7	Tethered one fingerlike lateral belly base moved upward	Segmental distribution central artery to lateral belly	Perivascular fibrosis and fibrosis of the tip	Two distinct free bellies base moved upward	Central artery to each belly	Fibrosis of the tip and the edges
8	Two distinct bellies fingerlike anterior tethered lateral	Severe atherosclerosis few long intramyocardial vessels none reaching the papillary muscle	Extensive fibrosis in the subjacent ventricular wall and less in the papillary muscle	Two short and thick bellies the medial free and fingerlike	Central artery to medial belly occluded	Fibrosis of the tip in the posterior belly and total fibrosis in the medial belly
9	Intermediate fingerlike central part; base moved upward	Segmental distribution central artery to the central portion	Fibrosis of the tip	Intermediate relatively free central portion base moved upward	One central artery and one long intramyocardial vessel	Normal
10	Intermediate; base moved upward	Segmental distribution	Normal	Intermediate two bellies, the medial one fingerlike base moved upward	Three sets of vessels central artery to medial belly*	Minimal fibrosis in the periphery and the tip

*[illegible] subendocardial plexus.

three broad categories, depending on the nature of attachment to the ventricular wall and the relative length of the body of the papillary muscle that protruded freely into the ventricular cavity The categories are (1) *completely tethered papillary muscle* i.e., a papillary muscle fully adherent to the subjacent ventricular myocardium and protruding very little into the ventricular cavity with few trabecular attachments (Figs. 1 and 2) (2) *fingerlike papillary muscle*, i.e., a papillary muscle with one third or more of the body protruding freely into the ventricular cavity with very few or no trabecular attachments (Figs. 1 and 3) and (3) *mixed type papillary muscle* i.e. a papillary muscle with part of the body protruding freely into the ventricular cavity but also with considerable trabecular attachments and tethering (Figs. 1 and 4) Both the anterolateral and the posteromedial papillary muscles usually had one or two distinct "bellies" of muscle (occasionally more than two) In the same heart the anterolateral papillary muscle may differ morphologically from the posteromedial one.

Just as the posteromedial and anterolateral papillary muscles can differ from each other in the same heart, when two or more bellies exist for any one papillary muscle these bellies can also differ morphologically The morphologic variations of the papillary muscles can be considerable.

The axis of orientation of the papillary muscles which is generally parallel to the long axis of the left ventricular cavity was found to be altered in the dilated hearts (see Fig 1 tethered papillary muscle) In the four hearts that showed left ventricular dilatation the bases of the papil-

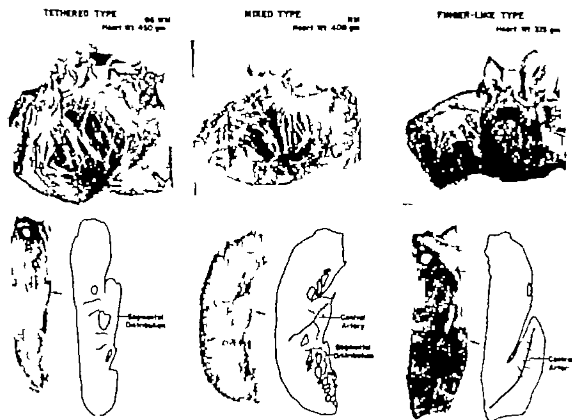


Fig. 1 Morphologic variations in the left ventricular papillary muscles tethered type, showing the papillary muscle completely adherent to the subjacent ventricular wall with very little free portion mixed type, showing central free portion but with considerable trabecular attachments fingerlike type, protruding freely into the left ventricular cavity

lary muscles had moved upward toward the atrioventricular valves. This has been observed previously by others[4,6] and is apparently related to unequal distribution of left ventricular dilatation which causes the apex and the anterolateral portion of the left ventricular wall to dilate much more than the septal portion of the ventricle

Arterial supply of the papillary muscles and the subjacent ventricular myocardium The main source of blood supply to the left ventricular papillary muscles has been well described by others.[7] Our findings in the ten hearts are in full agreement with these reports. The anterolateral papillary muscle receives branches from the anterior descending artery and either the diagonal left ventricular arteries or the marginal termination of the left circumflex artery. The posteromedial papillary muscle receives a variable supply from the left circumflex artery and/or branches of the right coronary artery. The larger epicardial branches of the coronary arteries course from the base to the apex of the heart sending branches (long relatively large penetrating branches and short, smaller ones) successively at right angles into the depths of the myocardium.

The stereoradiographs of the regions of the papillary muscles and subjacent ventricular myocardium clearly showed the arrangement of the intramyocardial vessels which supply the papillary muscles (Figs. 2 to 9). The vascular anatomy of these regions of the ten hearts studied is summarized in Table II. Some of the intramyocardial vessels were short and branched frequently and others were long and branched less frequently penetrating the subendocardial regions where they branched again and anastomosed with branches of adjacent penetrating arteries.

The papillary muscles, in general, were supplied by one or more of the long penetrating vessels which originated from the long arterial trunks lying on the epicardial surface of the heart. The course, spatial configuration and arrangements of the arteries supplying the papillary muscles appeared to be related to the gross morphologic state of the papillary muscles which they supplied. When the papillary muscle was quite free and fingerlike in configuration one of the large penetrating intramyocardial vessels arising from the epicardial arteries penetrated into the base



Fig. 2 Stereoscopic view of arterial distribution in tethered type papillary muscle.



Fig. 3 Stereoscopic view of arterial distribution in fingerlike papillary muscle.

of the papillary muscle coursing to the apex through the center of the muscle. After entering the muscle mass this artery divided into many branches in a dichotomous fashion forming a fairly rich network of anastomoses along the subendocardial area of the papillary muscle and especially near its apex. Arcuate vessels formed many of the anastomotic connections near the apex and subendocardial surface of the papillary muscle. This "central artery" measured as much as 900 microns in diameter at its entry into the base of the papillary muscle. A typical example is shown in Fig. 5.

The central artery was quite conspicuous by being large, long and terminal and branching in a dichotomous fashion. Papillary muscles or portions of papillary muscles receiving the central artery often had very few or no anastomotic connections with the extrapapillary subendocardial plexus. The tethered papillary muscles showed a segmental distribution of the long penetrating intramyocardial vessels (Fig. 5). These vessels measured approximately 160 to 320 microns in diameter and became somewhat enlarged after they entered the papillary muscles. They often showed rich anastomotic connections



Fig. 4. Stereoscopic view of arterial distribution in mixed type papillary muscle.

among themselves as well as with the extrapapillary subendocardial vascular plexus. As noted above, where the morphology of the papillary muscles varied between the anterolateral and posteromedial papillary muscles within the same heart, the associated vascular arrangement varied accordingly (Fig. 6).

The mixed type papillary muscle showed a combination of vascular arrangements (Fig. 7). If there was a distinct free fingerlike portion in a papillary muscle that otherwise showed mixed features, the free portion was supplied by a central artery (Fig. 7). When there were many trabecular attachments, the long penetrating intramyocardial vessels could be seen to course through them. This was common in the mixed type papillary muscle.

Histopathologic findings. The histopathologic findings are summarized in Table II. Severe coronary atherosclerosis of the epicardial vessels causing occlusion and scarring in the ventricular wall was present in two hearts. The penetrating intramyocardial vessels were occluded in such areas of scarring. There were short collateral arteries coursing parallel to the epicardium and endocardium. The subendocardial arteries and anastomotic vessels were dilated to establish effective collateral circulation (Fig. 8, *B*). Such changes have been noted also by others.[11,12]

In one of the hearts the papillary muscle was completely tethered to the subjacent ventricular wall and showed only minimal fibrosis compared to the extensive fibrosis which was present in the subjacent ventricular wall (Fig. 8, *C*, *D*, and *E*). Apparently the papillary muscle must have continued to receive adequate blood supply through the rich anastomotic connections with the adjacent extrapapillary subendocardial plexus (Fig. 8, *B*). In the other heart with extensive coronary atherosclerosis, there was scarring of the entire medial belly of the posteromedial group of papillary muscles. Some scattered scarring was also noted in other portions of the same group of posteromedial papillary muscles. It is interesting that the scarred medial belly of the posteromedial group of papillary muscles was the most free portion anatomically and that there was a central

64 WM
Heart Wt 450 gm
TETHERED PAPILLARY MUSCLE
Segmental Distribution

77 WM
FINGER-LIKE PAPILLARY MUSCLE
Central Artery

Section through Central Artery

Fig 5 \ al t of left ntric lar papillary muscles tethered type with segmental distribution of long pene t g nt n c dial vessels fingerlike papillary muscle with a central artery

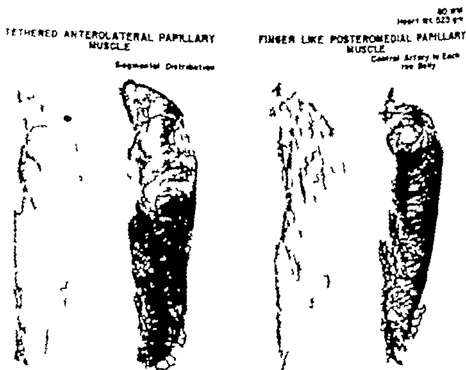


Fig 6 Variations in morphology and the corresponding variations in arterial vasculature in the two groups (anterolateral and posteromedial) of papillary muscle with segmental distribution posteromedial papillary muscle with two fingerlike bellies, each with its own central artery

artery which was occluded at the base of the papillary muscle. Subendocardial connections were present in the other portions of the papillary muscles but not in the fibrotic medial belly (Fig 9 *A B* and *C*) Fibrosis at the tip of the papillary muscle, however appeared unrelated to the type of vascular arrangement (Fig 7 and Fig 9 *F*)

Discussion

In the ten human hearts studied the arterial vasculature of the papillary muscles seemed to be related to the gross morphologic characteristics of the papillary muscle. Two predominant types of arrangement of the long penetrating intramyocardial vessels were observed. The finger like papillary muscle received a large *central artery* at its base, arising from one of the epicardial arteries in that region. The central artery was long terminal, and measured as much as 900 microns at its entry into the papillary muscle. It then coursed through the muscle mass toward the apex, dividing dichotomously to form a network of anastomoses after the fourth and fifth divisions, supplying almost the entire papillary muscle. Such freely protruding papillary muscles showed very few or no anastomotic connections with the extrapapillary subendocardial plexus. One can easily imagine how patency of this vessel in such papillary muscles could be

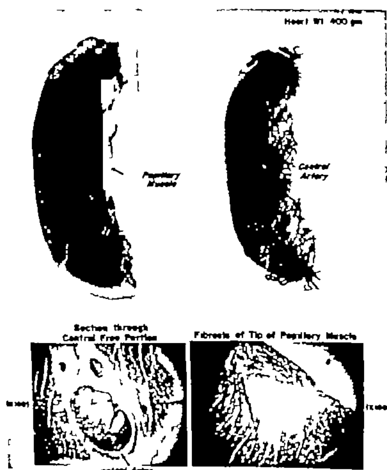


Fig 7 Vascular arrangement in mixed type papillary muscles with the usual penetrating long intramyocardial vessels and central artery supplying the central free belly Fibrosis of the tip is seen in spite of apparent rich blood supply (lower right panel).







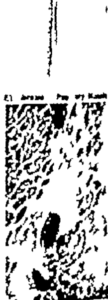


Fig. 8. [illegible] papillary muscle and the subjacent ventricular wall in severe coronary atherosclerosis. (*A*) [illegible] muscle with some scarring and noticeable gross scarring of subjacent ventricular wall. (*B*) [illegible] the occlusion of long penetrating intramyocardial vessels. Short collaterals running parallel to [illegible] and endocardium are noticeable. Papillary muscle is predominantly supplied by subendocardial connections (extra- and intrapapillary). (*C*) Photograph of a section through the papillary muscle and [illegible] ventricular wall showing extensive fibrosis of subjacent ventricular wall and scattered fibrosis of papillary muscle. (*D*) Section through subjacent ventricular wall showing extensive fibrosis. (*E*) Scattered fibrosis [illegible] the papillary muscle.

very crucial for such a vessel is not only most peripheral in the coronary arterial tree but also it distributes itself to a considerable area which has very little anastomotic connection with the extrapapillary subendocardial plexus. On the other hand the tethered variety of papillary muscles had a *segmental* distribution of the long penetrating intramyocardial vessels. The branches of these vessels not only made connection with one another but also had rich anastomotic connections with the extrapapillary subendocardial plexus. The papillary muscles which showed combined features had a *mixed* type of vascular arrangement. When the papillary muscles had thick trabecular attachments some of the long intramyocardial vessels were seen to course through them. When the papillary muscles of either tethered or mixed type had a distinct free belly or a freely protruding portion this free belly or portion received a central artery whereas the tethered portions received a segmental type of arterial supply. This constitutes a mixed pattern of blood supply.

It seems reasonable that such anatomic variations would play a large role in the functional alterations as well as the pathologic changes in the papillary muscles which accompany disturbances in circulation to the region of the papillary muscles. Rich extrapapillary subendocardial connections as observed in the papillary muscles that are relatively or completely tethered to the subjacent ventricular wall would help to perfuse the papillary muscles even in the presence of occlusion or narrowing of the larger epicardial vessels feeding into them. In such cases, there may be very little functional alteration and very minimal pathologic change in the papillary



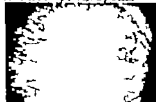
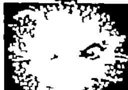




Fig 9 Arterial vasculature gross pathology and histopathology of papillary muscles. (A) Mixed type of posteromedial papillary muscle with free fingerlike medial belly showing scarring. (B) Radiograph of the region shown in (A) illustrating occlusion of long penetrating transmyocardial vessels. Medial belly is almost devoid of vascularity whereas there are few subendocardial connections in the other portions. (C) Section through the fingerlike medial belly showing extensive fibrosis. (D) and (E) Tethered papillary muscle showing segmental distribution of vessels. (F) Fibrosis of the tip of the tethered papillary muscle. (G) Perivascular fibrosis is also noted.

muscles, in spite of obstructive arterial disease in adjacent areas with extensive damage to the subjacent ventricular wall. This was observed in one of the hearts studied (Fig 8). On the other hand occlusion or narrowing of the central artery or of the epicardial artery from which the former arises could easily result in dysfunction or even total and irreversible damage of the papillary muscle that is predominantly supplied by such a vessel. Such was the case in one of the hearts examined (Fig 9 A B and C). The distal fibrosis seen in papillary muscles, however seems to be unrelated to the anatomic variation, at least in this study and probably only reflects the tenuous nature of the vascular perfusion to this region in all papillary muscles.

Summary

The arterial vasculature of the papillary muscles of the left ventricle was studied in detail in ten human hearts, using the technique of stereoscopic arteriography followed by detailed histologic examination. The arrangement of the arterial vasculature of the papillary muscle seemed to be related to the gross morphologic characteristics of the papillary muscle. Two predominant types of arrangement were noted. Papillary muscles that were fingerlike received a large central artery which coursed through the entire papillary

muscle to its apex dividing dichotomously to supply the papillary muscle. Such papillary muscles had very few or no anastomotic connections with the extrapapillary subendocardial plexus of vessels. The papillary muscles that were completely tethered to the subjacent ventricular wall had a segmental distribution of the long penetrating intramyocardial vessels. The papillary muscles of the mixed type had a combination of both types of vascular arrangement. Both the mixed type and the completely tethered papillary muscles with the segmental pattern of arterial distribution had many anastomotic connections with the extrapapillary subendocardial plexus. These anatomic variations could have a considerable influence on functional alterations as well as pathologic changes in the papillary muscles accompanying disturbances in arterial circulation to the region of the papillary muscles.

The assistance of Dr. Adrian Reed is greatly appreciated.

REFERENCES

1. Burch, G. E., DePasquale, N. P., and Phillips, J. H.: Clinical manifestations of papillary muscle dysfunction, Arch. Int. Med. 112:112, 1963.
2. Phillips, J. H., DePasquale, N. P., and Burch, G. E.: The electrocardiogram in infarction of the anterolateral papillary muscle, Am. Heart J. 66:338, 1963.
3. Estes, E. H., Dalton, F. M., Entman, M. L., Dixon, H. B., II, and Hackel, D. B.: The anatomy and blood supply of the papillary muscles of the left ventricle, Am. Heart J. 71:356, 1966.
4. Fulton, W. F. M.: Arterial anastomoses in the coronary circulation. I. Anatomical features in normal and diseased hearts demonstrated by stereo-arteriography, Scot. M. J. 8:420, 1963.
5. Hale, A. R., and Reed, A. F.: Studies in cerebral circulation. Methods for the qualitative and quantitative study of human cerebral blood vessels, Am. Heart J. 66:226, 1963.
6. Grant, R. P.: Architectonics of the heart, Am. Heart J. 46:405, 1953.
7. Gross, L.: The blood supply to the heart in its anatomical and clinical aspects, New York, 1921, Paul B. Hoeber, Inc., Medical Book Division of Harper & Row Publishers.
8. Spalteholz, W.: Die arterien der Herzwand, Leipzig, 1924, S. Hirzel.
9. James, T. N.: Anatomy of the coronary arteries in health and disease, Circulation 32:1020, 1965.
10. Fulton, W. F. M.: The coronary arteries: arteriography, microanatomy and pathogenesis of obliterative coronary artery disease, Springfield, Ill., 1965, Charles C Thomas, Publisher.
11. Fulton, W. F. M.: The dynamic factor in enlargement of coronary arterial anastomoses, and paradoxical changes in the subendocardial plexus, Brit. Heart J. 26:39, 1964.
12. Estes, E. H., Entman, M. L., Dixon, H. B., II, and Hackel, D. B.: The vascular supply of the left ventricular wall. Anatomic observations plus a hypothesis regarding acute events in coronary artery disease, Am. Heart J. 71:58, 1966.

Changes in the body's QRS surface potentials produced by alterations in certain compartments of the nonhomogeneous conducting model

Robert H. Bayley, M.D.
*John M. Kalbfleisch, M.D.***
*Paul M. Berry, Ph.D.****
Oklahoma City, Okla.

In 1927 Canfield, working for W. H. Craib, gave electrocardiography its first mathematical solution of the potential produced by the heart beat. The model used by Canfield was that of a homogeneous insulated spherical conductor and the field source was that of a centric dipole. Canfield's presentation was extremely brief and, because of its considerable importance to many areas of electrocardiography, Bayley has recently presented the general solution of which Canfield's equation is a particular part. The second important extension of this model was made by Wilson and Bayley[3] when they used this same model but changed the field source to an *arbitrary eccentric* dipole. Another extension was made by Frank[4] when he used the (radial) eccentric *double-layer* in the place of the (radial) eccentric dipole as a field source. The *homogeneous* model was then replaced by the *nonhomogeneous* conductor in 1962 by Bayley and Berry. Here, the eccentric dipole was used as a field source in the spherical conductor. Using this model certain of the surface potentials were computed. In 1964 Bayley and Berry, working with experimental models, developed the mathematical theory for the arbitrary double-layer in the nonhomogeneous (compartmental) 2-space conductor. For experimental convenience and for economy it was necessary to use the 2-space circular model. Finally, in 1965 Bayley and Berry[8] presented the mathematical solution for the analogous 3-space model. They used the arbitrary (radial) eccentric double-layer.

It is axiomatic to expect that, as the model becomes more realistic, the complexity of the associated mathematical formulations should increase. However, it is not necessary for the physicians to understand the mathematics in order to understand the model and appreciate the clinical applications for which the modle

From the Department of Medicine, the University of Oklahoma Medical Center, Oklahoma City, Okla.
Supported in part by National Institutes of Health Grants HE-01499 and 4-K6-HE-14174, by the Oklahoma State Heart Association, American Heart Association, and the Computer Facility of the University of Oklahoma Medical Center.
Received for publication Aug. 15, 1968.
*Professor of Internal Medicine, University of Oklahoma School of Medicine.
**Assistant Professor of Medicine, University of Oklahoma School of Medicine, Teaching Scholar of the American Heart Association.
***Research Associate, Mobil Research and Development Corp., Field Research Laboratory, P. O. Box 900, Dallas, Texas.

Vol. 77, No. 4, pp. 517-528, April, 1969

is used The purpose of this report is to describe the Bayley Berry[8] model from a physician's point of view and to demonstrate some of its clinical implications.

Model description

All of space involving three variables $(X\ Y\ Z)$ is subdivided into seven compartments six compartments are interior to the surface of the conducting body and the seventh is exterior (Fig 1) Each compartment has its separate resistivity ρ_1 ρ ρ_7 (Table I) There are six interfaces S_1 S_2 S_3 S_6 which separate the seven compartments. For further details see legend of Table I Any point on

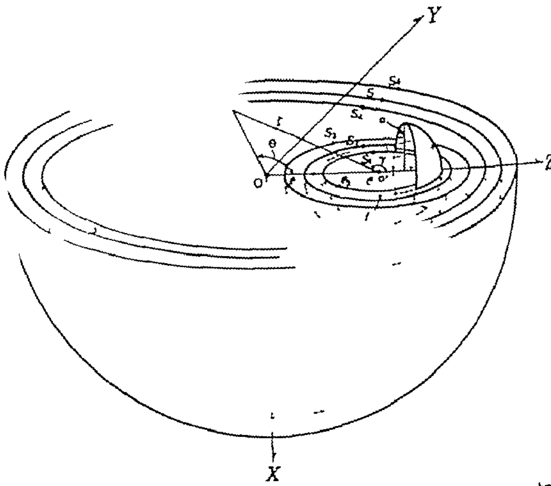


Fig. 1 The nonhomogeneous isotropic (or inhomogeneous) spherical conductor is divided into seven subregions each having its own specific resistivity ρ_7 They are shown separated by spherical surfaces S_1 S_6 It is at each of these interfaces that the potential and the normal components of the current must be continuous. The radii of these surfaces are denoted by R R_6 Heart center o' is taken eccentric with respect to "body center" with origin at "body center" through an arbitrary distance C The spherical coordinates with respect to the "heart center" of the "body center" are (θ Φ) for the field point and (θ Φ) for the field source and, with respect to the "heart center" the spherical coordinates are (r γ ξ) for the field point and $(r_o\ \gamma_o\ \xi_o)$ for the field source or rim of the double-layer cap which is concentric about the Z-axis with boundary of radius The "heart wall" region is oriented between S and S_2 and contains the arbitrary double layer field source or electromotive surface of ventricular activation. The dipole cap is oriented upon the fictitious spherical surface f at which the normal currents are continuous. When the compartment of resistivity ρ_4 is empty with no pericardial fluid, the anterior surface of the heart S_3 is made tangent with the inner surface S of the torso shell simply by taking the appropriate value for o' which when added to R gives value equal to R_4. Consequently the drawing is highly schematic for purposes of clarity and one is not permitted to conclude that a massive lung region separates the heart from the inner surface of the chest walls, when indeed they are tangent under computation in the absence of pericardial fluid or other abnormal pericardial environment (see text).

the body surface is described in the standard spherical coordinates (R_6, θ, ϕ) (Fig 1) The volumes of the six body compartments are made realistic by proper choice of the radii R R_6. The body surface potentials V are computed for seven points about the left hemithorax at the level of the cardiac ventricles that is, along the equator of the body sphere moving in the transverse of YZ plane. All such points are defined by $P(R_6, \theta, 0)$ The central angle θ ranges from $\theta = 0$, anterior through $\theta = 180°$ posterior in increments of 30° (Table II)

*Table I The compartmented conductor**

Conductor		Ohm /cm.
Heart-cavity blood	(ρ_1)	160
Heart wall region	(ρ_2)	400
Pericardial environment	(ρ_3)	ρ_3
Lung region	(ρ_4)	000
Muscle-bone region of torso shell	$(\rho\ )$	360
Skin fat-pad region of torso shell	(ρ_6)	2 000
Exterior medium	(ρ_7)	∞

*The values of ρ_1 ρ_6 are given in ohms/cm. When no pericardial fluid is present ρ_3 ρ_2 and the radius R for the pericardium equals R_2 the radius of the epicardial surface and $V = V$ that is, the potentials for the pericardial sac are nonexistent in the sense that they are the same as those described by V for the heart wall. In the computer program, ρ_1 is computed in terms of the normal hematocrit (0 435)

The nonhomogeneous disturbance factor

This factor denoted by D is new in the formulation of electrocardiographic potentials. It is a function of the geometry of the (six) body compartments and of the (five) ratios of the six specific resistivities of each compartment (see Appendix) The insulated conducting body ρ_7 is taken as infinite (Table I) and consequently does not enter the nonhomogeneous disturbance factor D_n. Alterations in any one or more of the specific resistivities ρ ρ_6, or in the geometry of any one or more of the compartments of the conducting body will alter the potential at every point of the body internally and on its surface. In particular the surface potentials V are changed by alterations of this kind which enter through D the nonhomogeneous disturbance factor Furthermore, if all the specific resistances ρ ρ are made equal (not zero or infinite) D becomes unity and V is then the appropriate surface potential for the homogeneous model.

The field source

As indicated in the introduction the field source for QRS is an electromotive double-layer similar to that observed during ventricular accession. It is, therefore necessarily located in the "heart wall" region of the model. As will become apparent its exact location within the heart

*Table II Decreases in ρ for heart cavity blood**

θ	H 42.5 V†	H 32.5 V	H 22.5 V	H 12.5 V‡	↗
0°	60 2	64 8	68 8	72 3	20
30°	42 6	46 0	49 0	51 6	—
60°	10 6	11 7	12 6	13 5	—
90°	− 8 8	− 9 3	− 9 8	−10 3	—
120°	−16 5	−17 9	−19 2	−20 3	—
150°	−20 6	−22 5	−24 2	−25 7	—
180°	−21 8	−23 8	−_5 7	−27 3	26

*θ is the angle made by the radius vector R_6 and the Z-axis taken anteriorly through the heart center As θ increases by increments of 30° in the transverse plane, the potentials V indicated are given about the left hemithorax. Column 2 shows the potentials with normal hematocrit (42.5 per cent) Column 6 refers to per cent increase of the anterior and posterior potentials shown in column 5 The correction factors for moment and double-layer location are given for columns 2 and 5, the first ones being normal nonhomogeneity and the second showing the change in these factors for the lowest value of hematocrit. In each column heading, the hematocrit is followed by the potential V
†$(1/D_1)$ 47 $(D_1/D_0) = 1.27$
‡$(1/D_1) = 0.34$, $(D_1/D_0) = $ 43

wall region is not of great importance for this report primarily because its orientation remains unchanged throughout all computations of the surface potentials [illegible] presented in the tables. For computational convenience, the boundary of the accession double layer is taken to be of circular form symmetric about the Z axis and with a radial double layer in the anterior half of the heart wall region. Positive poles of the double layer are directed radially outward from heart center o (Fig. 1). Time is confined to the QRS-interval and the heart's field is symmetrical about the Z axis. On the surface of the conducting body positive potentials are oriented anteriorly and negative potentials posteriorly. The clinical situation may be likened to the apex of R in the Z lead of the axial lead system when the positive axis of Z is chosen in an anterior direction. It is likened to the apex of Q in this lead system when the positive axis is taken [illegible] the conventionally proper way. [illegible] any case the instant chosen for [illegible] putation is such that ventricular [illegible] is predominantly radial and [illegible] result [illegible] anterior direction. At some [illegible] in the QRS-interval [illegible] ventricular accession will be predominantly radial and in a resultant posterior direction. The surface potentials [illegible] of the conducting body are in part determined by the field source space orientation of the boundary or boundaries of the accession double layer and by its strength or total moment. However, the field source is independent of the nonhomogeneous disturbance factor in the sense that the former is independent of the geometry of the heart wall region. No alterations in the geometry of the heart wall region are included in this report and no changes are made in the specific resistivity ρ_2 of the heart muscle.

Nonrealistic feature. The most striking deficiency in the model is the unrealistic contour of the interfaces. If the contour of the torso shell along the circular arc of computation of the surface potentials were made elliptical for a better anatomical fit, these potentials would show relative increases anteriorly and posteriorly and decreases in the lateral segments because of proximity changes. If the model were elongated in the vertical direction for better fit to the body trunk, decreases of the potentials would occur over the superior and inferior surfaces of the torso shell where no surface potentials are computed. The liver-diaphragm region of the model is neglected wherein the resistivities are of low value. Its inclusion would cause decreases in the potentials of the right hemithorax and on the inferior body surfaces where no potentials are computed and the changes in surface potentials elsewhere would be affected to a lesser degree.

In the Gabor-Nelson[11] theory for finding the moment $\vec{M}$ and coordinates $(\bar{X}, \bar{Y}, \bar{Z})$ of the resultant heart vector at a given QRS instant by using the surface potentials, they used a homogeneous conducting body. Our introduction of the nonhomogeneous conducting body makes the moment $\vec{M}$ go over into $(\vec{M}/D_n)$ wherein $n = 1$ in D_n and the coordinates are each multiplied by (D_n/D_n) where $n = 1$ and $n = 2$ in the numerator and denominator respectively. We have called $(1/D_1)$ and (D_1/D_2) the nonhomogeneous corrections for the moment and for the location coordinates of the equivalent heart vector respectively. They are simply the reciprocals of those that occur with computations under the proposed nonhomogeneous state. When the resistivities ρ_1 [illegible] ρ_4 are taken equal to ρ_2 for heart muscle both correction factors become one or unity and consequently they do not disturb the Gabor-Nelson equations since the conducting body is assumed to be homogeneous.

The heart wall region is not considered to have greater radial than tangential resistivity although this anisotropy is known to exist.* Inasmuch as normal ventricular accession is predominantly radial rather than tangential, the combined [illegible] tional effects are minimized and the resistivity ρ_2 for the heart wall region is used as a compromise (Table I). Furthermore

*Personal communication, 1964, and publication by Reynolds, E. W., and Weller, D. A.: An experimental study of the electromotive forces of the heart, Am. Heart J. 69:[illegible], 1965. Also see reference 7.

in spite of the differences in the specific resistivities of the radial as compared with tangential directions of measurement in the ventricular myocardium (anisotropy) the accession wave expanding from a single focus of stimulation behaves as a uniform closed double-layer until one surface of the myocardium (endocardium or epicardium) is reached

Methods

Computer program Formula (32) for the Bayley Berry[8] model (see Appendix) is programmed for an accuracy which includes an error not exceeding 0 1 per cent. This required the summations to be carried through the first 40 terms where the convergence factor is about 0 548 raised to the eightieth power

Results

Decreased values for ρ_1 The computer program enters the hematocrit H for the heart cavity blood and computes the value for ρ by the relation[12]

$$\rho = \frac{70(f + H)}{f(1 - H)} \qquad (1)$$

Here 70 Ω cm is the resistivity for serum at normal body temperature and f is the form factor for the shape of the nonconducting red blood cells. If red blood cells are of spherical form the form factor for f is a numerical value two, but if the shape is that for normal red cells f is taken as 1.35 and if the normal hematocrit H is 42.5 per cent ρ computes at a normal value of 160 Ω cm This value for the resistivity of normal whole human blood was first given by H C Berger and later confirmed by Rush.[13] For decreasing values of H (see Table II row 1) the values of V_m the potentials are observed to increase. The maximal values for V (column 5) show an increase of 20 to 25 per cent when compared with those computed for the normal hematocrit (column 2) Also Table II shows a decrease in the correction factor $(1/D)$ and an increase in the correction factor (D_1/D_2) for the resultant moment and for its coordinates respectively

Empirical clinical observations have shown that precordial QRS voltage may show an increase in certain cases of anemia which may or may not display cardiomegaly but there has been no attempt to quantitate such changes using isolated changes in the hematocrit.

Increased values for ρ_1 Further results are shown by Tables III through VI and their legends. All changes in potentials V are to be compared (per cent increase or per cent decrease) with the relative normals given in column 2 Table II on which the normal percentage change is based It should be emphasized that the most important part in these tables is the direction of the arrows indicating that the changes in surface potentials are increased or decreased. Of course, only relative

Table III *Increases in* ρ *for heart cavity blood**

θ	H 52.5 V†	H 62.5 V	H 72.5 V	H 82.5 V‡	H 92.5 V	← ↘
0°	54 8	48 4	40 7	31 2	19 1	
30°	38 7	34 0	28 4	21 5	13 5	68 2
60°	9 3	7 9	6 3	4 4	2 1	
90°	− 8 1	− 7 2	− 6 2	− 4 8	− 3 1	
120°	−14 8	−12 8	−10 5	− 7 8	− 4 1	
150°	−18 4	−15 8	−12 8	− 9 3	− 3 1	
180°	−19 4	−16 6	−13 5	− 9 7	− 5 3	75 5

*Stepwise decreases in potentials are shown for stepwise increases in the hematocrit of heart cavity blood When H = 72.5 per cent, the correction factor for the resultant dipole moment is about unity and that for the orientation of the double-layer boundary is about unity for H = 93 Column 7 shows the per cent decrease of the anterior and posterior potentials in column 6. When increases in the hematocrit occur the changes of potential are more striking than with decreases (Table II)
†$(1/D_1)$ 1.04 (D_1/D_2) = 1.1.
‡$(1/D_1)$ 2 41, (D_1/D_2) = 1.04.

Table IV Pericardial fluids

#	Pericardial fluids (ml) 100		250		500		1000		1500		2000	
	B	S	B	S	B	S	B	S	B	S	B	S
0°	52 8	4 7	45 3	31 9	39 3	25 1	33 7	19 9	30 6	17.6	21 6	14 9
30°	37 9	31 1	33 8	24 1	30 1	19 4	26 7	15 9	21 9	14.3	23.8	13 1
60°	10 7	9 4	10 4	8 0	10.3	7 0	10.4	6 4	10 6	6.2	10 9	4 3
90°	− 7 4	− 5 7	− 6 2	− 4 1	− 5 1	− 3 1	− 4.0	− 2.3	− 3 3	− 1.8	− 2 1	− 1 5
120°	−15 3	−12 9	−14 1	−10 4	−13 2	− 8 7	−12.5	− 7.5	−12.2	− 7 1	−13 1	− 4 9
150°	−19 4	−16 7	−18 3	−13 7	−17 3	−11.6	−16 7	−10.2	−16 6	− 9 7	−16.8	9 4
180°	−20 6	−17 8	−19 5	−14 7	−18 5	−12 5	−17 9	−11 0	−18 0	−10.6	−18 2	−10 3
	9	4	17	40	25	50	31	58	33	61	34	62

B stands for blood and S for serum Columns show computed potentials. Bottom row shows average decrease of normal percentage of negative potentials These averages are influenced by changes in heart center eccentricity made to accommodate the asymmetric distribution of pericardial fluid (see text)

*Table V Increased resistivity in the lung region of the model**

#	3,000		ρ_4 4,000		ρ_4 5,000		ρ_4 6,000	
	V	%	V	% ↘	V	% ↘	V	% ↘
0°	48 5	19	40 4	33	34 5	43	30 0	50
30°	34 7		29 0		24 9		21 9	
60°	9 1		8 0		7 0		6 2	
90°	− 7 0		− 5 6		− 4 7		− 4 1	
120°	−13 7		−11 6		−10 1		− 8 8	
150°	−17 4		−14 9		−13 0		−11 5	
180°	−18 5	15	−15 9	27	−13 9	36	−12 3	43

*The normal value for ρ_4 is about 2,000 Ω cm The per cent decrease shown is compared with the corresponding values of V computed with normal resistivities The increased values for ρ_4 are shown in row 1 and the corresponding potentials V for given ρ_4 are shown in columns 2 4, and 6 The per cent decrease as compared with normal potentials anteriorly and posteriorly are shown in columns 3 5 and 7 Normal values for V appear in column 2, Table II It is noted that diffuse increases of lung resistivity produce progressive decreases in the surface potentials. Note direction of arrow

values are meaningful and herein must be considered only approximate.

With established polycythemia vera, high values of the hematocrit might be expected to diminish the increased QRS voltage associated with left ventricular hypertrophy which otherwise may be ascribed to the increased work of moving a fluid of high viscosity On the other hand late QRS voltages with right bundle branch block or left bundle branch block are associated with electromotive forces that are oriented largely in a tangential rather than a radial direction In these instances increases in ρ_1 are known to increase rather than decrease these surface potentials[41]

Pericardial effusions When the radius vector R to the pericardial surface is made equal the radius vector R to the epicardi

*Table VI Decreases resistivity in the lung region of the model**

θ	ρ_4 1,500		ρ_4 1,000		ρ 500	
	V	% ↗	V	% ↗	V	% ↗
0°	67.7	12	75.6	26	77.2	28
30°	47.6		52.6		53.3	
60°	11.2		11.4		9.6	
90°	−10.1		−11.6		−12.4	
120°	−18.0		−19.3		−18.4	
150°	−22.2		−23.3		−21.5	
180°	−23.4	8	−24.5	12	−22.3	2

*See legend Table V Per cent increases of V anterior and posterior compared with normal, are shown columns 3 5 and 7 Potentials V for given values of ρ_4 are shown in columns 2, 4, and 6

surface, and when $\rho_3 = \rho_2$ (as in Table I) no effective pericardial cavity exists in the Bayley Berry model and heart eccentricity is taken which permits the anterior outer surface of the heart and inner surface of the chest wall to be tangent. With the presence of pericardial fluid we have $R > R_2$ and $\rho_3 < \rho_2$. The resistivity ρ_3 is now assigned a value of 70 Ω cm. equivalent to that of serum For comparison with these results (Table IV) computations are repeated with $\rho_3 = 160$ Ω cm. the value for pericardial hemorrhage of like quantities. The accumulations of pericardial fluid are permitted to range from 100 through 2,000 ml. (top row Table IV) In the model, the eccentricity of heart center o necessarily decreased as the quantity of pericardial fluid increased. The symmetrical distribution of pericardial fluid about the heart wall region is unrealistic.

Increased values for ρ_4. In the model ρ is the specific resistivity of the lung region (Table I) The surface potentials V of the conducting body are decreased as the resistivity of the lung region is arbitrarily increased (Table V) As ρ approaches an increase of three times normal, the maximal potentials (column 7) approach a 40 to 50 per cent decrease (column 8, Table V)

It may be assumed that, as diffuse pulmonary emphysema progresses much conducting tissue of the lungs is lost and consequently the specific resistivity of these tissue increases. However this isolated event is obviously a marked simplification of the matter

Decreased values for ρ_4. The results are shown in Table VI where decreases of ρ of the lung region effect increases in the surface potentials V of the conducting body As ρ_4 approaches one fourth of its normal value the increase of precordial potentials, column 6 $\theta = 0°$ approach 28 per cent of their normal value (column 7) The increase in back potentials (columns 3 5 7 $\theta = 180°$ Table VI) is not striking and averages only about 7 per cent for the range of ρ computed

Table VI is interpreted as showing loss of normal insulation effect of the lungs upon the heart's electrical field with respect to its increased field strength in the outermost compartments of the conducting body

The torso shell with ρ and ρ_5. When the muscle borne component is increased by two times its average normal thickness, the potential V anteriorly ($\theta = 0$) is reduced by nearly 50 per cent and when the resistivity ρ is reduced from 360 Ω cm to 300 Ω cm the reduction in V is somewhat greater than 50 per cent of normal Increasing the normal skin fatpad in thickness by N times normal, where $N = 2$ 4 and 6 reduces the anterior potential V by increments of approximately 13 per cent. ρ_5 would not change with increasing obesity

Compartment two between interfaces S and S_2. The 'heart wall' shell is most

complex and can only be considered briefly in this report. On the order of accession defined earlier a dead zone of anteroseptal infarction was superimposed. The radius of the infarct had to be increased by one third to equal the anterior potential V ($\theta = 0$) produced in the homogeneous case; that is, normal nonhomogeneity apparently diminished the radius of the anteroseptal infarct by one third of the homogeneous (actual) case. Here, the size of the dead zone was such as to reduce the apex of normal R in Leads V_1–V_3, or V_4 to a baseline value. The positive Z axis of the formulae (see Appendix) is arbitrary and can be taken through any anterior V-lead which contains the largest R deflection. If the largest R voltage is in V_4, the infarct (which reduces this R to the baseline) might be called anterolateral rather than anteroseptal.

Discussion

Models initially crude in concept have repeatedly served a valuable role in the exploration of the unknown. It is in this conceptual type approach that the Bayley-Berry model of a nonhomogeneous (compartmented) conducting body of the heart's electrical field is offered. The mathematical results described are highly accurate for the model considered. The important generalized extension to nonsymmetric fields is presented in the appendix, and this model may be regarded as disposing of the early homogeneous conducting models which have dominated electrocardiography since 1927. Their obvious importance to clinical electrocardiography is initiated with this report.

It is emphasized that five of the six compartments of the model have been exploited briefly here. The reason is because of the greater complexity of compartment two. A discussion of the important heart wall region is deferred for the most part to the problem which necessarily deals with asymmetrical fields (Appendix formula no. 2). When this has been done, the important combinational changes involving two or more compartments simultaneously will be undertaken. It appears to us highly likely that further meaningful clinical implications will result.

By contrast, the multipole theory of [illegible] net pole strength obviously covers the problem from a completely different point of view. Here it is required that numerous instantaneous body surface potentials be measured in a highly accurate manner in order to appropriately enter the surface integrals involved. When all is completed, using this approach, one may safely state that one or more multipoles of higher tensorial rank than that of the dipole undoubtedly exists. These are the quadrupole and possibly the octopole, for potentials measured close to the smallest spherical surface which surrounds the centric heart with ? poles for the multipole located at heart center. This vague result is replaced in our analysis by 2/2 double-layer boundaries of accession in the eccentric heart-wall and under Helmholtz's law of superposition we commence with precise distribution of electromotive forces in the heart using an assumed equation[3] and computing for the potentials of one boundary at a time which [illegible] "capping" or closing the remaining boundaries. When the potentials for each boundary computed separately are added for the instant considered, the result for all boundaries acting together at that instant is obtained. The unsatisfactory multipole approach is too general in its results which can safely be predicted by the very nature of cardiac excitation; moreover, it appears to us that little of clinical value is added by such a proof, inasmuch as no clues are permitted as to the actual distribution of electromotive forces within the centric heart during either accession or regression. On the contrary, solutions of the kind offered here commence with a precise distribution of ventricular electromotive forces in the important QRS complex, and in turn result in a knowledge of "body surface potential changes of a kind which are meaningful to the clinical electrocardiographer and which may not be obtained by other means (see Appendix). While it is true that many of the results reported here in the tables could have been predicted by the clinical cardiologist, some of them could not have and the problem of introducing combinational changes is for the most part quite beyond the level of our present reasoning even by the expert

electrocardiologist. Consequently the general approach offered here becomes more and more well defined by methods involving bipolar and unipolar direct leads.

Summary

1 Extended conceptual models can be made to give useful clinical information of a kind not currently obtainable by any other means. The model considered here in part disposes of the 40-year-old homogeneous models, all of which must still hold a respected place in electrocardiographic interpretations since their introduction in 1927

2 The six compartments are discussed in isolated changes one at a time to illustrate their effects on body surface potential V_s.

3 The important equation for a more generalized model may be found in the Appendix together with all elements necessary for programming on a computer and heretofore to be used for computing body surface potentials by superpositional changes in any one or all of the compartments.

4 Finally it should be emphasized that changing the geometry or the appropriate resistivity ratio of any one compartment alters the potential at every point within and on the surface of the insulated conducting nonhomogeneous model as demonstrated in the Appendix.

Appendix

The model is a compartmented conductor in which each compartment is assigned a specific resistivity ρ_1 ρ_2, ρ_3 ρ_7 (Table I) The spherical conducting body contains six compartments and a seventh compartment is the exterior region. The center o of the conducting body is taken as the origin of the X Y Z-coordinates and the spherical coordinates in such a way that the (Z) polar axis passes through o′ the heart center located at Q_1 $(C\ 0\ 0)$ in the spherical coordinates (Fig 2) Separating the seven compartments are six nonintersecting spherical interfaces of radii R_1 R_2, R R_6. The three innermost interfaces are concentric on Q $(C\ 0\ 0)$ and the outermost three interfaces are concentric about body center o The radii of these interfaces are adjusted to give realistic compartmental volumes. The field source is a uniform double-layer electromotive surface of one circular boundary per computation of the potentials. The Helmholtz theorem of superposition permits an arbitrary number of boundaries in the heart wall region to be used one per computation and the surface potentials at any given point are merely added for the final result computed from any number of boundaries computed separately The radius of a given boundary is denoted by a with a boundary center at the space point Q $(b\ \theta_a\ \Phi_a)$ in the spherical coordinates with reference to heart center o at Q $(C\ 0\ 0)$ (Fig 2) The distance from o to any point on the boundary of the double layer is denoted by h (Fig 2)

The potential V desired is at any point $P(R_6,\ \theta\ \Phi)$ in spherical coordinates referred to body center o of S the outermost interface (Fig 2) Bayley and Berry[7,8] have shown that it is sufficient to obtain the solutions for V V_2, V V_6 everywhere in each of the seven compartments, two solutions being required for the heart wall region. At any one of the interfaces the boundary conditions are continuity of the potentials $V = V'$ and continuity of the normal currents $(\partial V/\rho\ \partial n) = (\partial V'/\rho'\ \partial n)$ The normal currents are also continuous at the fictitious interface oriented at the electromotive surface. Whenever the field source is bounded (no poles at infinity) it is required that V vanish at infinity All functions for V_1, V_2, V V_8 are harmonic that is $\nabla^2 V = 0$ $i = 1,$ 8. The conditions are sufficient to determine the potential everywhere as a unique point function with no arbitrary constants. When the radius vector r from o to any point P $(r\ \theta\ \Phi)$ in 3-space is made equal to R_6 in either of the solutions V or V of Berry's[1] general solution the desired surface potentials on S are obtained at once The result is

*If the boundary of the electromotive surface is noncircular πa^2 is replaced by its actual area and h is taken as an average distance from Q_1 $(C,\ 0\ 0)$ to the boundary points, and b is taken as the distance from Q_1 $(C\ 0\ 0)$ to the centroid of the area included by the boundary If the boundary is nonplanar more complicated approximation replacements will be required by using two or more planar boundaries.

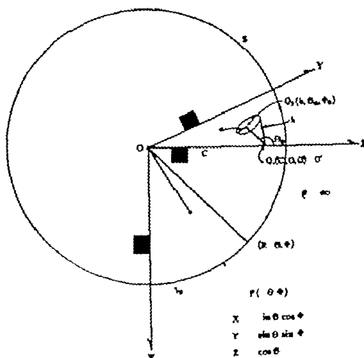


Fig 2 Origin of the X Y Z coord nates is at the center of the conducting body The polar axis Z is taken through Q (C 0 0 heart center σ' which is in turn the origin of the spherical coordinates (b θ Φ). is the radius of the bou dary of the double-la er nd Q_1 (b θ_0, Φ) is the center of this boundary t a distance b from σ' S is the outermost terface where t potential V is computed by equation (2) for any surface point P (R_0, θ, Φ). The import nc of solution of this model is emphasized by the argument that all body potentials of the electrocardiog m ori n the heart muscle may be described as produced by one or more double layer constructed t taneous nd in sequence the boundaries of which are located on the *surface* (endocardial and/or epicardial) of the heart muscle mass. These potentials are therefore *independent* of the order of activation (accession nd egression) of the muscle units between these surfaces. The order of activation of the heart surface u it onseque tly determines the form and location of the boundary or boundaries of the double-layer surface or surface respectively These in turn therefore determine the form of the ECG insofar as the field source enter the potential form lation

$$V\ (R_0\ \theta\ \Phi) = \frac{2\pi M\alpha\ \rho_s}{k^2} \sum \sum \sum$$

$$D\ \frac{(\epsilon_{m-k})\ (2n+1)\ (n-m+k)\,!}{n(n-k+1)\ (n+m-2k)\,!\ k!} \times$$

$$\left(\frac{k}{R_0}\right) \left(\frac{C}{k}\right) P \rightarrow \left(\frac{b}{k}\right) P'^{m}_{\rightarrow}(\mu_0)\, P^{m-}(\mu) \times$$

$$\text{Cos}\,[(m-k)\ (\Phi - \Phi)] \qquad (2)$$

wherein μ denotes the cosine of the angle θ' and μ denotes the cosine of the angle θ and D is the nonhomogeneous disturbance factor described elsewhere[8] The prime on P' $\left(\frac{b}{k}\right)$ denotes differentiation with respect to the argument b/k (ϵ_{m-k}) is the Neumann factor It is unity for $m - k = 0$ and is 2 for $m - k > 0$. If C is zero, the only nonzero term in the summation on k is for $k = 0$ If the axis of the double-layer circular rim is concentric on the Z-axis, the only nonzero term in the summation is for $m = 0$ Under these conditions equation (2) reduces to either of equations (32) which are used for computations of tables in this report and which have been published[8] but are reproduced below for the reader's convenience. They are

$$\left.\begin{array}{c} V = \dfrac{2\pi\alpha M}{R_0^2} \sum D\ \dfrac{2n+1}{n(n+1)} \\ \left(\dfrac{r}{R_0}\right)\ P\ (\mu_0) P\ (\mu) \\ \text{or} \\ V = 2\pi M \sum D \left(\dfrac{r_1}{R_0}\right)^{+} \\ [P_{-}(\mu) - P_{+}(\mu_0)]\, P\ (\mu) \end{array}\right\} \quad (3)$$

If in these equations (32)[*] $\rho_1 = \rho_2 = \rho_3 = \rho = \rho_4 = \rho$ $0 < \rho < \infty$ $D = 1$ E. Frank's[4] equation for the homogeneous conducting body is obtained. It remains to define D in equations (2) and (3) above. For this purpose we have

$$D = A \; B_n B_n^3 B_n^2 B_n$$

wherein the right hand side is the product of five interdependent coefficients. Explicitly they are

$$A = \left[1 - \frac{n+1}{n} \frac{1 - (\rho_4/\rho)}{\frac{n+1}{n} + (\rho_4/\rho)} \left(\frac{R}{S}\right)^{2n+1}\right]^{-1}$$

$$B^1 = \frac{2n+1}{n} \frac{R_3^{2n}}{\alpha_n + \frac{n+1}{n} (\rho_3/\rho_2)\beta}$$

wherein

$$\alpha_n = R_3^{2n} + \frac{n+1}{n} C_n^3 R_3^{2n+1}$$

$$\beta_n = R_3^{2n+1} - C_n^3 R_3^{2n+1}$$

$$B^2 = \frac{2n+1}{n} \frac{R_4^{2n+1}}{\alpha_n + \frac{n+1}{n} (\rho_2/\rho)\beta_n^2}$$

$$C_n^2 = \frac{\alpha_n - (\rho_3/\rho_2)\beta_n^2}{\alpha_n + \frac{n+1}{n} (\rho_3/\rho_4)\beta_n^2}$$

wherein

$$\alpha_n = R_4^2 + \frac{n+1}{n} C_n^2 R^{2n+1}$$

$$\beta_n^2 = R_4^{2n+1} - C_n^2 R_4^{2n+1}$$

$$B_n^2 = \frac{2n+1}{n} \frac{R_4^{2n}}{\alpha_n + \frac{n+1}{n} (\rho/\rho_3)\beta^2}$$

$$C_n^2 = \frac{\alpha_n - (\rho/\rho_4)\beta^1}{\alpha + \frac{n+1}{n} (\rho/\rho_4)\beta^1}$$

wherein

$$\alpha_n = R_3^{2n+1} + \frac{n+1}{n} C_n^1 R_4^{2n}$$

[*] Here, is equivalent to the distance h, equation (2), and, in equation (3) enters indirectly through and θ

$$\beta^1 = R_4^{2n+1} - C_n^1 R_4^{2n+1}$$

and finally

$$B^1 = \frac{2n+1}{n} \frac{R_n^{2n+1}}{\alpha_n + \frac{n+1}{n} (\rho_1/\rho_4)\beta^1}$$

$$C_n^1 = \frac{\alpha_n - (\rho_1/\rho_4)\beta_n^1}{\alpha_n + \frac{n+1}{n} (\rho_1/\rho_4)\beta_n}$$

wherein

$$\alpha_n = R^{2n} + \frac{n+1}{n} R_4^{2n}$$

$$\beta_n^1 = R_4^{2n+1} - R_4^{2n+1}$$

It is desirable to use true anatomical compartmental geometry in computing surface potentials. However the development of the necessary computational techniques is a project that is now economically unjustifiable. In the meantime the inside out approach indicated by equation (2) and its appropriate numerous variations appear practical for a large number of useful clinical implications.

REFERENCES

1. Canfield, R. On the lectrical field surrounding doublets and its significance from the standpoint of Einthoven equations, Heart 14 102 1927
2. Bayley R. H. Heart conducting media and unipolar leads, Oklahoma State Med A. J p. 562 Aug 1965
3. Wilson, F. N. and Bayley R. H. The electric field of an eccentric dipole in homogeneous spherical conducting medium, Circulation 1:84 1950
4. Frank E. A comparative analysis of the eccentric (radial) double layer representation of the human heart, Am. Heart J 46:364 1953.
5. Bayley R. H. and Berry P. M. The electrical field produced by the eccentric current dipole in the nonhomogeneous conductor Am. Heart J 63:808, 1962.
6. Bayley R. H., and Berry P. M. Body surface potentials produced by the eccentric dipole in the heart wall of the nonhomogeneous volume conductor Am. Heart J 65:200, 1963.
7. Bayley R. H., and Berry P. M. The arbitrary electromotive double-layer in the eccentric "heart" of the nonhomogeneous circular lamina, I.E.E.E. Trans. B.M.E. 11 137 1964
8. Bayley R. H. and Berry P. M. Changes produced in the resultant "heart" vector by the nonhomogeneous volume conductor with normal specific resistivities Vectorcardiography—1965 Amsterdam The Netherlands 1966 North-Holland Pub. Co. p. 109

9. McFee, R., and P rungan, A. An orthogonal lead system for clinical electrocardiography Am Heart J 62:93 1961
10. Bayley R H Special purpose computer for measurement of the mean ECG axes in Vectorcardiography–1965 Amsterdam The Netherlands, 1966 North-Holland Pub Co p. 98
11. Gabor D and Nelson, C V Determination of the resultant dipole of the heart from measurements on the body surface, J Appl Physics 25:413 1954
12. Rush, S Abildskov J A and McFee, R Resistivity of body tissues at low frequencies, Circulation Res. 12:40, 1963
13. Rush S. Personal communication, 1962 A limiting form of Clerk Maxwell equation (17) Electricity and magnetism ed. 3 Oxford, 1892 Oxford University Press p 440
14. Brody D A A theoretical analysis of intracavitary blood mass influence on heart lead relationship Circulation Res. 4:731, 1956
15. Nelson, C. V Chatterjee, M Angelakos, E. T and Hecht H H Model studies on the effect of intracardiac blood on the electrocardiogram Am Heart J 62:83 1961
16. Conrad L. L., and Cuddy T E. The influence of boundary conditions on the amplitude of R and other accession potentials in leads from the ventricular wall, Circulation Res. 8:82, 1960.
17. Bayley R. H Applications of modern electrocardiographic theory to the interpretation of electrocardiograms which represent myocardial disease, Am. Heart J 26:769 1943
18. Berry P M Mathematical theory of electrocardiography Ph.D Thesis, Department of Mathematics, the University of Oklahoma, Norman, Okla., 1968.

Case reports

An unusual site of ventricular pacing occurring during the use of the transvenous catheter pacemaker

*Jack W Spitzberg**
Mayer Milstoc M.D
Arthur R. Wertheim M D
New York N Y

Ever since extrinsic pacing of the heart was initiated in 1870[1] and applied clinically in 1952 more and more lives have been prolonged with the aid of permanent electrical pacemakers. As a sequel to their increased use numerous abnormalities of pacemaker function have arisen. Among these malfunctions are perforation of the ventricular myocardium displacement of the electrode, defects in the pacemaker itself breakage of electrodes, and changing myocardial thresholds. [11] In the case to be presented however the pacemaker was functioning well in a surprising location and this malposition was evident in retrospect by a review of roentgenograms and electrocardiograms (ECG) These findings may alert physicians in the future to this abnormality in electrode position.

Case report

M. W was 75-year-old widow who entered Goldwater Memorial Hospital in 1967 for care of her chronic obstructive lung disease with cor pulmonale and for maintenance of an internal bipolar pacemaker I 1961 the ECG showed right axis deviation (RAD), sinus tachycardia of 110 with P R interval of 0.15 second, QRS of 0 12 second right bundle branch block (RBBB) and multiple premature ventricular contractions. I 1964 she was admitted to hospital for fainting spells and the ECG showed RAD with nodal rhythm and short periods of asystole. Her heart reverted to normal sinus rhythm on intensive pulmonary regimen. Because of mild cardiac failure, digitoxin was administered in 1965 and maintained.

I December of 1965 she had sudden two-second nonfocal seizure. The ECG showed a 2 1 A V block with periods of complete heart block. This conduction disturbance was thought to be secondary t digitalis toxicity and the digitalis was discontinued. Nevertheless in J uary 1966 she had 2 syncopal episodes. The ECG showed complete heart block with ventricular rat of 20 due to an idioventricular pacemaker A catheter pacemaker (Medtronic-Chardack Bipola No. 51407) was inserted and connected to subcutaneous battery pack. Each pace artifact was followed by ventricular contraction t rate of 80 The next day however only 50 per cent of the impulses were conducted with periods of asystole after every other artifact, and she paced t rate of 40. N therapy was instituted and several days she began to follow perfectly t a rate of 80

The patient did well until 14 days later when she returned to the clinic after several more syncopal episodes. The ECG showed that the heart failed to respond to 25 per cent of the pacemaker artifacts It was felt that the pacemaker pulse generator was defective and temporary intravenous pacemaker

From the Columbia University Research Service, the Department of Medicine, Columbia University College of Physicians and Surgeons, the Department of Pathology New York University Medical Center Goldwater Memorial Hospital, Welfare Island, New York, N Y 1001
This study was supported by Grants U- 017 and U-1542 from the Health Research Council of the City of New York.
Received for publication Dec 26 1967
*Fourth year medical student

was passed through the brachial vein w th the tip lodged in the right ventricle These new electrodes wer connected to an external power source and the original lectrodes were disconnected from the defec tive pulse generator The electrodes however re mained in place After the repa the battery box was connected back t the orig nal lectrodes nd the temporary electrodes wer emoved She followed the new pacemaker unit perfectly

The patie t was discharged hom nd did well u til 1½ years late he he was dm tted to Goldw ter Memorial Hospital f the fi t time for dyspnea associated th her d tage emphysema. She had had no pr blem lated to pacemaker func tion since her discharg D ring her 3 month tay t Goldwater Memorial H spital sh became more dependent upon esp tor nd d ring her last week of l f became ar anotic dev loped in creasing râles fev nd died ne pectedl An ECG shortly fter de th h wed the pa emaker to be function ng (the t t ere present but were not followed b t la esponse)

Postmortem examination

An aut psy was performed and the fol lowing fi dings were noted cor pulmonale marked pulmonary emphysema and fibrosis focal bronchopneumonia of the left lung, and moderate generalized arteriosclerosis. Special attention was given to the pace maker to determine if any complication had interfered with its proper function. As the pacemaker s electrode was traced from the chest wall a surprising position was found. The electrode entered the venous system via the right jugular vein. It passed down into the superior vena cava and entered the right atrium It continued its course along the posterior wall of the atrium and at the site of the opening of the coronary sinus it entered into an enlarged ostium of the middle cardiac vein and passed down the vein The tip of the wire was seen near the apex of the heart over the left ventricular wall about 6 cm. from the opening of the coronary sinus. The transparency of the distended wall of the vein permitted visuali zation of the entire length of the wire and the electrodes (Figs 1 and 2)

Discussion

The heuristic value of this report lies in the fact that in retrospect an abnormality



Fig 1 Anterior view of the heart looking t the opened right atrium nd entricle. Note pacemaker lectrode entering coronary si us (rrow) to extend int the middle coronary ein



Fig 2 Posterior iew of the nopened heart showing the electrode hich ca be seen through the wall of the middle cardia ei (rrows).

of catheter placement might have been predicted by roentgenograms and ECG's. The films showed the catheter tip displaced posteriorly 10 cm. from the sternum in the lateral projection. With proper placement, the electrode should have pointed straight toward the apex of the heart and should have been only a few centimeters behind the sternum.

The ECG's, however gave the best clue to the abnormality. As one can see from Fig. 3 when the patient was pacing from the epicardial surface, the ECG revealed a pattern simulating an intraventricular conduction defect (IVCD) with the left ventricle being depolarized first. The impulse was obviously not spreading through the heart by way of the conducting system but was transmitted directly to the myocardial fibers from the electrode on the epicardial surface. The resulting picture was that of a ventricular conduction defect with a pattern similar to that produced by a RBBB though the mode of arrival of the stimulus is entirely different. The ventricular activation time of 0.10 second in V_1 and only 0.04 second in V_6 supports the suspicion of abnormal position. However, more definite support came when the patient was temporarily paced from another electrode this

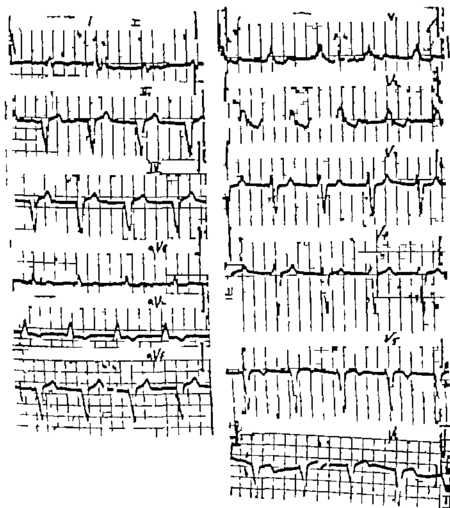


Fig. 3. Permanent pacemaker in position 1, the middle cardiac vein. Note RR and prolonged ventricular activation times in V1 and the wide S in Lead I. Because the stimulus is delivered to the left ventricle first, the tracing resembles a RBBB.

time in the expected position the endocardial surface of the right ventricle Then the ECG changed (Fig 4) the stimulus being delivered to the endocardium of the right ventricle as expected The activation time in V was much shorter than with the previous pacemaker and the configuration of the complexes changed to that of an IVCD in which the right ventricle was being stimulated first. This pattern is similar to that produced by a LBBB

Mower and associates[11] presented 4 ca-

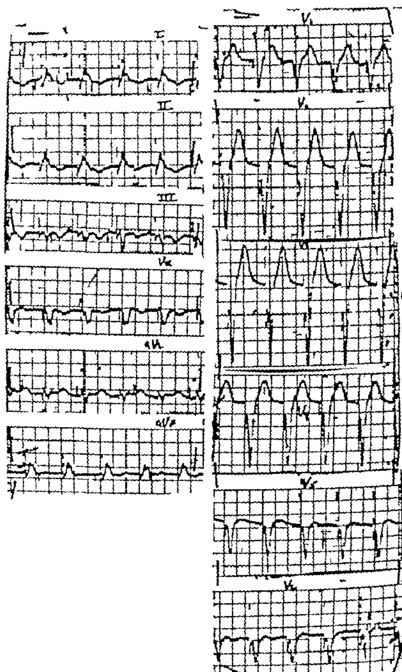


Fig 4 Temporary pacing of the right ventricle while permanent pacemaker being repaired. Note the absence of the S in Lead I and of the RR' sequence in V The stimulus in this case is being delivered to the right ventricle and the tracing shows IVCD resembling that of a LBBB

nual cases in which patients pacing from the right ventricle showed a picture of RBBB He suggested that the pacemaker stimuli in some instances might affect the conducting system to render the A V node and the RBB refractory to centrifugal con duction while permitting a stimulus to travel retrograde up the RBB to the A V node and down the LBB stimulating the left ventricle first. This possibility how ever was remote in our patient for her disease had previously rendered her RBB nonconductive and subsequent ECG s gave evidence of bilateral bundle branch block. As seen above a picture of RBBB may also occur when pacing arises from the epi cardial surface of the left ventricle.

Zucker and co-workers[13] showed that in dogs the electrical potential needed to pace a ventricle was only 0 25 to 0 5 volts, while in the coronary sinus much higher voltages were required In 2 patients who were paced from a site near the sinus, somatic muscular contractions accompanied the higher volt age requirements, and heart response was only intermittent. In contrast this pa tient s heart responded well at necropsy the pacemaker was checked and found to have a voltage of 6.3 volts and a rate of 65 8 per minute. The venous wall did not impede the electrical impulses nor was there any myocardial damage at the site of the electrodes. There were no thrombi in the vein nor on the electrodes, and the wall of the vein was not damaged

While the pacemaker worked well despite its abnormal location this may not always be true. A persistent picture of RBBB with a pacemaker presumably in the right ven tricle should suggest penetration of the interventricular septum from right to left retrograde conduction up the right bundle and down the left, location of the active tip at the membranous septum with electrical penetration through to the left side or as was seen here, an abnormal position on the epicardial surface.

Summary

A patient is presented who maintained the electrocardiographic pattern of an intra ventricular conduction defect similar to a RBBB for 18 months after an artificial pacemaker was thought to have been placed transvenously into her right ventricle At autopsy the electrodes were found to have traversed the coronary sinus and entered the middle cardiac vein. This resulted in pacing from the epicardial surface of the left ventricle To our knowledge, this ab normal location of a pacemaker electrode has not previously been reported Electro cardiographic evidence for malpositioning is presented The possible significance of a persistent RBBB in patients being paced from the right ventricle is discussed

REFERENCES

1 Parsonnet, V Zucker I. R Gilbert, L and Meyers, G H. A review of intracardiac pacing with specific reference to the use of a dipolar electrode, Progr Cardiovas. Dis. 6:472, 1964.
2 Zoll, P M Resuscitation of the heart in ventricular standstill by external cardiac stimulation, New England J Med 247 768, 1952.
3 Furman, S. Complications of pacemaker therapy for heart block, Am. J Cardiol. 17:439 1966.
4 Hellerstein, H. E. and Hornstein, T R The runaway artificial pacemaker Ohio State Med. J 62:907 1966.
5 Bartley F D and Wheat, M W J Pacemaker problems, Florida M A. 53:498, 1966.
6. Lister J W Escher D Furman, S Schwedel, J Stern, E and Damato, A Heart block method for rapid determination of causes of pacing failure in artificial pacemaker systems, Am J Cardiol. 18:64 1966.
7 Gordon, A. J Catheter pacing in complete heart block, J.A M A 93 1091 1965.
8 Craig R. H., Parker B and Foster R. P Cardiac pacing its problems and solutions, J Louisiana M Soc. 118:437 1966.
9 Kantrowitz, A. Implantable cardiac pacemaker New York Acad. Sc. 111:981 1964.
10. Parsonnet, V Gilbert, L. Zucker I R. and Asa, N Complications of the implanted pacemaker J Thoracic & Cardiovas. Surg. 45:801 1963
11 Mower M. M Aranaga, C. E and Tabatznik, B. Unusual patterns of conduction produced by pacemaker stimuli, Am. Heart J 4:24 1967
12. Nathan, D A Perforation during indwelling catheter pacing, Circulation 33 128, 1966.
13 Zucker I R., Parsonnet, V Gilbert, L. and Asa, N Dipolar electrode in heart block. J.A.M A 184:549 1963

Fatal acute rheumatic fever in childhood despite corticosteroid therapy

A note on the spectrum of childhood rheumatic fever

D. Luke Glancy, M.D.
Rashid A. Massumi, M.D.
William C. Roberts, M.D.
Bethesda, Md., and Washington, D. C.

The incidence of death in childhood from rheumatic heart disease has been declining in the United States for 3 decades. The role of adrenocorticotrophic hormone and adrenal corticosteroids in the continuing decline in the mortality rate during the past 2 decades has been debated widely and remains uncertain. Nevertheless, death from rheumatic carditis is now uncommon in children treated with these agents and is rare during an initial attack of rheumatic fever. Such occurred, however, in 2 children recently studied by us. Each died of different causes which represent widely separate bands in the spectrum of rheumatic heart disease in children.

Report of patients

Patient 1. A 3-year-old girl was hospitalized following an upper respiratory infection because of a skin rash which had features of both erythema marginatum and urticaria, and arthritis of both ankles. Fever (101 F.), pharyngitis, and a systolic ejection-type murmur at the left sternal edge were present. A leukocyte count was 22,000 per cubic millimeter, anti-streptolysin O titer 625 Todd units, corrected sedimentation rate 32 mm. per hour, and C-reactive protein reactive. In the hospital, the temperature rose to 103° F., arthritis of both knees developed while that of the ankles subsided, and the systolic murmur became loudest at the cardiac apex and radiated to the left axilla and back. The fever and arthritis responded favorably to aspirin and prednisolone (50 mg. per day), but on her eighteenth day of hospitalization, the twentieth day of illness, she developed dyspnea, tachypnea, tachycardia (170 per minute), a ventricular gallop, hepatomegaly, and died.

Necropsy (A67-286) disclosed generalized cardiomegaly (weight, 105 grams; expected weight, 60 grams), slight thickening of all 4 cardiac valves, and histologically pancarditis with numerous Aschoff bodies (Figs. 1 and 2).

Patient 2. A 9-year-old girl was well until 1½ years before death when she developed typical signs and symptoms of acute rheumatic fever. She remained in the hospital during the entire 1½-year period. A loud murmur typical of mitral regurgitation was heard when she was first examined and remained thereafter. Congestive cardiac failure was present throughout the illness, but it appeared to be less

Received for publication Feb. 13, 1968.
*Staff Associate, Section of Pathology, National Heart Institute, National Institutes of Health, Bethesda, Md. 20014.
**Cardiologist, District of Columbia General Hospital, and Chief, Cardiopulmonary Laboratory, George Washington University Division of Medicine, District of Columbia General Hospital, Washington, D. C.
***Chief, Section of Pathology, National Heart Institute, National Institutes of Health, Bethesda, Md.



Fig. 1 The heart of Case 1 Opened right trium (R A), right ventricle (R.V), and slightly but diffusely thickened tricuspid valve. b Opened left atrium (L.A) left entricle (L V), and lightly but diffusely thick ened aortic (A V) and mitral valves. Above the posterior mitral leaflet (P) the left trial endocardium is thickened and irregular (MacCall s plaque) Photomicrograph showing pleomorphic infiltrate with large mononuclear cells, similar t those in Aschoff bodies, in pulmonic valve cusp. (Hematoxylin and eosin stain, X200.)

severe when the child was receiving prednisone (up to 40 mg daily) and more severe when this medication was discontinued. First degree heart block was present until the last weeks of lif when trial fibrillation developed. She died unexpectedly

Necropsy (A67-185) disclosed generalized cardiomegaly (eight, 320 grams expected eight, 115 grams)· severe fibrosis of the mitral valve with a fixed, severely incompetent orifice left atrial jet lesion normal aortic, tricuspid and pulmonic valves and normal pericardium Histologically most myocardial fibers of each cardiac chamber ere hypertrophied, but no inflammatory cells or Aschoff bodies ere found (Fig 3).

Comment

Although acute rheumatic fever occurs in patients under 4 years of age, it does so infrequently and we are aware of only 14 children[4-13] who like Patient 1 died of acute rheumatic fever before 4 years of age and who were found at necropsy to have Aschoff bodies. Photomicrographic demonstration of the Aschoff bodies was presented n 5 of them.[4-7] Aschoff bodies are said to be absent during the first few weeks of acute rheumatic fever[14] and adrenal corticosteroids have been reported to decrease markedly the cellular reaction in rheumatic myocarditis.[14] The heart of Patient 1 however contained numerous, typical Aschoff bodies and an exuberant cellular reaction despite a total symptomatic illness of only 20 days and treatment with large doses of prednisolone

In contrast to Patient 1 whose death was primarily due to acute rheumatic myocarditis, Patient 2 died of severe mitral regurgitation. Although it is reasonable to believe that acute rheumatic carditis was present at the beginning of her illness, no inflammatory lesions were present at necropsy 1½ years later and except for hypertrophy the myocardium was normal. Cardiac failure in children with rheumatic heart disease suggests that the rheumatic carditis is still active[14] and in Patient 2 this suggestion was supported by the transient but apparently beneficial effects of prednisone. Her cardiac failure however was due to an operatively correctable mechanical defect, mitral incompetence, and mitral valve replacement might have been lifesaving Rheumatic mitral regurgitation has been considered



Fig 1 For leg

Fig. 2. Photomicrographs in Case 1. A, Inflammatory nodule in the left atrial endocardium consisting of a necrotic center surrounded by large mononuclear cells and a peripheral zone of polymorphonuclear neutrophils. B, Posterior mitral leaflet containing fibrinoid material, polymorphonuclear neutrophils, and large mononuclear cells. C and D, Aschoff bodies consisting of altered collagen surrounded by large, mononuclear (Anitschkow) cells and giant cells. (Hematoxylin and eosin stains. A, ×160; B and C, ×400; and D, ×6.3; each reduced 25 per cent.)

Fig. 3. Heart of Case 2. Opened left atrium showing the incompetent mitral valve orifice (O) and the contracted anterior (A) and posterior (P) leaflets. The dashed line encloses an area of thickened endocardium on the posterior wall. This lesion almost certainly resulted from the impact of a jet of blood regurgitated through the incompetent mitral orifice from the left ventricle during ventricular systole. The myocardium beneath this lesion showed histologic features of severe degeneration, but this was the only portion of myocardium that showed changes other than hypertrophy. B, Close-up of the opened mitral valve. Both leaflets and the chordae tendineae are thick and shortened. No calcium deposits are present. Ant. and Post., anterior and posterior leaflets, respectively. A.L. and P.M., anterolateral and posteromedial papillary muscles, respectively.

---

a benign lesion in certain selected groups of patients,[17] but in Patient 2 it caused death 1½ years after the initial episode of acute rheumatic fever.

REFERENCES

1. Massell, B. F., Amezcua, F., and Pelargonio, S.: Evolving picture of rheumatic fever. Data from 40 years at the House of the Good Samaritan, J.A.M.A. 188:287, 1964.
2. A joint report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council of Rheumatic Fever and Congenital Heart Disease, American Heart Association: The evolution of rheumatic heart disease in children. Five year report of a cooperative clinical trial of ACTH, cortisone, and aspirin, Circulation 22:503, 1960.
3. Legue, R. B., and Hurst, J. W.: Rheumatic fever during the first five years of life and its differentiation from endocardial fibrosis, Am. J. M. Sc. 223:618, 1952.
4. McIntosh, R., and Wood, C. L.: Rheumatic infections occurring in the first three years of life, Am. J. Dis. Child. 49:835, 1935.
5. Fischer, A. E.: Rheumatic heart disease at one year, Am. J. Dis. Child. 48:590, 1934.
6. Schwarz, H.: An unusual case of acute rheumatic fever in an infant, Contributions to the medical sciences in honor of Dr. Emanuel Libman, New York, 1932, The International Press, vol. 3, p. 1061.
7. Murphy, G. E.: The characteristic rheumatic lesions of striated and of non-striated or smooth muscle cells of the heart, Medicine 42:73, 1963.
8. Elgren, L. A.: Juvenile rheumatic fever. Report of a case in an infant two years of age, Am. Heart J. 16:363, 1938.
9. White, P. D.: The incidence of endocarditis in earliest childhood, Am. J. Dis. Child. 32:536, 1926.
10. Denzer, B. S.: Rheumatic heart disease in children under two years of age. Report of three cases, J.A.M.A. 82:1243, 1924.
11. Schroeder, L. C.: Observations on the etiology and pathology of chorea minor, J.A.M.A. 79:181, 1922.
12. Friedberg, C. K.: Diseases of the heart, ed. 3, Philadelphia, 1966, W. B. Saunders Company, p. 1321.
13. Smith, A. deG.: Rheumatism and its manifestations in children under five years, Arch. Pediat. 39:799, 1922.
14. Baggenstoss, A. H., and Saphir, O.: Rheumatic disease of the heart. In Gould, S. E., editor: Pathology of the heart, ed. 2, Springfield, Ill., 1960, Charles C Thomas, Publisher, p. 655.
15. Golden, A., and Hurst, J. W.: Alterations of the lesions of acute rheumatic myocarditis during cortisone therapy, Circulation 7:318, 1953.
16. Massell, B. F., Fyler, D. C., and Roy, S. B.: The clinical picture of rheumatic fever: Diagnosis, immediate prognosis, course, and therapeutic implications, Am. J. Cardiol. 1:436, 1958.
17. Jhaveri, S., Czoniczer, G., Reider, R. B., and Massell, B. F.: Relatively benign "pure" mitral regurgitation of rheumatic origin. A study of seventy-four adult patients, Circulation 22:39, 1960.

Clinical pathologic conference

Satyanarayana Rao, M.D.
Ray C. Anderson, M.D.
Russell V. Lucas, Jr., M.D.
Aldo Castaneda, M.D.
Carlos Ibarra-Perez, M.D.
Michael E. Korns, M.D.
Jesse E. Edwards, M.D.
St. Paul, Minn.

DR. SATYANARAYANA RAO: This female infant was evaluated at 8 months of age because of cyanosis, a cardiac murmur, and failure to thrive. She was born of an uncomplicated pregnancy, weighing 5 pounds 11 ounces. Anal atresia and a rectovaginal fistula were noted at birth. At 3 months of age, congenital dislocation of the right hip and 5 thoracic hemivertebrae were recognized and a cardiac murmur was heard for the first time. Subsequently, the patient fed poorly and failed to thrive. There were episodes of cyanosis of the lips and nail beds, especially with crying, and later persistent cyanosis became evident. Marked retardation of physical growth and development were evident.

Physical examination when the patient was 8 months old revealed a small, poorly developed, mildly cyanotic female infant below the third percentile for both height and weight. The lungs were clear. The impulse of the apex of the heart was palpable 1 cm. inside the left mid-clavicular line. There were no thrills or heaves. The first and second cardiac sounds were loud and single. A Grade 2/6 nonspecific murmur occupying the first half of systole was heard over the left sternal border. A Grade 2/6 mid-diastolic rumbling murmur with presystolic accentuation was heard just inside the apex. No ejection click or additional heart sounds were noted. Auscultatory blood pressure was 94 mm. Hg systolic and 60 diastolic in the right arm. Simultaneous flush blood pressures were 85 mm. Hg in the right arm and right leg. The edge of the liver was palpable 2 cm. below the right costal margin. Also noted were thoracic scoliosis, a shortened left leg, internal rotation and a coxa vara deformity of the right hip, as well as anal atresia with a rectovaginal fistula.

The electrocardiogram (ECG) (Fig. 1) revealed normal sinus rhythm, an axis of minus 145 degrees, and evidence of right ventricular hypertrophy and right atrial enlargement. Q waves were present in Lead V₁ but not in V₆. The vectorcardiogram indicated right ventricular hypertrophy. Thoracic roentgenograms (Fig. 2) demonstrated minimal cardiomegaly, left atrial enlargement, a prominent main

From the Departments of Pediatrics, Surgery, and Pathology, University of Minnesota, Minneapolis, and the Department of Pathology, the Charles T. Miller Hospital, St. Paul, Minn.
This study was supported by Public Health Service Research Grant 5 R01 HE-05694 and Research Training Grant 2 T1 HE-05570 from the National Heart Institute, and by the Dwan Family Fund, University of Minnesota Hospitals, Minneapolis, Minn.
Address: Pathology Department, Charles T. Miller Hospital, 125 West College Avenue, St. Paul, Minn. 55102.

pulmonary arterial segment, and increased pulmonary venous markings.

Dr Anderson you saw this patient initially What was your impression?

DR. RAY C ANDERSON At the time, our primary diagnosis was congenital mitral stenosis with additional intracardiac mal formations to account for the apparent right-to-left shunt. The diastolic murmur was the most significant auscultatory finding and it was on this finding and the roentgenographic evidence of pulmonary congestion that we based our diagnosis of mitral valvular obstruction. We had no firm idea as to what the additional malformations were although right to-left shunting through a ventricular septal defect or a patent ductus arteriosus statistically would have been the most likely The right ventricular hypertrophy shown on the ECG was considered to be evidence of right ventricular hypertension Definitive studies were indicated and therefore arranged.

DR. RAO Right-sided cardiac catheterization, right ventriculography and a pulmonary arteriogram were performed (Table I) During catheterization, the catheter tip was passed easily into the right atrium, right ventricle and pulmonary artery in that order Despite numerous attempts the tip could neither be passed across the atrial septum nor did it cross the ventricular septum It was also impossible to obtain a valid pulmonary arterial wedge pressure On numerous occasions, the catheter passed easily from main pul

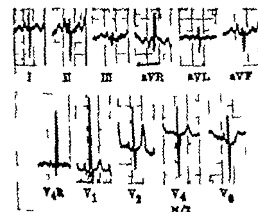


Fig. 1 The ECG reflects right atrial enlargement and right ventricular hypertrophy



Fig 2 Thoracic roentgenograms A Frontal view Pulmonary venous congestion is apparent. Kerley B lines were present with original film. The pulmonary arterial segment is prominent and there is evidence of biatrial enlargement. B Lateral view Evidence of right ventricular and left atrial enlargement.

monary artery th ugh a patent ductus arteriosus int th descending aorta. On 2 occasions the theter upon entering the descending aorta p sed obliquely upward toward the right sh ulder

As you suspe ted Dr Anderson pressures in the pul nary artery were ele vated In fact t e pressures in the pulmona y art r ight ventricle and descending rt l equal magnitude A signifi nt in n oxygen saturation occurred the ht ventricle and there was no furthe rease in the level of oxygen the theter was advanced into the pulm na y tery The oxygen satura tion in th descending aorta was equal to that in th pulm nary artery

Dr Luca would you interpret these data an l r late the to the angiocardiograms

DR R Luc s Jr In essence these l m l left to-right shunt at the v tr l l l an apparent right to-left hu n h luctus arteriosus an l qua l t l pressures in the right v t l pulm nary artery and d l nt We can presume that the tri l septu wa ntact since there u l lt ight shunt at atrial level d the theter tip directed from the infer ven va failed to enter the left atrium

In add tion the course of the catheter tip est blished the presence of a patent ductus arteriosus and its further course from descending aorta to the right shoulder was characteristic of origin of the right subclavian artery from the descending aorta.

These hemody iamic data taken at face value suggest the combination of large ventricular septal defect patent ductus arteriosus and coarctation of the aorta proximal to the luctus arteriosus This combination of lesions would be consistent with the observed left to-right shunt at the ventricular level and right to-left shunt at the level of the patent ductus Fully saturated blood obtained from the ascending aorta w uld have supported this diagnosis. U fortunately the arterial sample obtained from the right arm reflects the saturation of the descending aorta (on the basis the origin of the right subclavian artery from the descending aorta) and we do not have a sample from the ascending aorta.

Table 1 Summary of data obtained during cardiac catheterization

Site	Pressure (mm Hg)	Oxygen saturation (%)
Descending aorta	100/50 (31 73)	72
Pulmonary artery	90/65 (31-83) 120/70 (31-90)	70
Right ventricle	115/0-8	72, 80
Right atrium	31 5	34, 35
Superior vena cava	—	36
Inferior vena cava	—	33 ?
Right subclavian artery	100/68 (31-82)	64

*First pulmonary arterial pressure obtained upon withdrawal of catheter from descending aorta, second recorded immediately before withdrawing the catheter into the right ventricle.

On the other hand the data are equally compatible with the presence of a bidirectional shunt at the ventricular level. In such a case the ascending aorta would contain desaturated blood and the presence of desaturated blood in the descending aorta would not imply right to-left shunt through the patent ductus arteriosus. A bidirectional shunt at the ventricular level implies significantly elevated pulmonary vascular resistance This can appear in an isolated ventricular septal defect In the infant however this degree of elevation of pulmonary vascular resistance suggests an obstructive lesion in the left side of the heart as a contributing factor The clinical information also suggested an obstructive lesion in the left side of the heart. The absence of left ventricular hypertrophy places the obstructive lesion at the mitral valve or proximal to it.[3] (i.e. mitral stenosis, supravalvular stenosing ring of the left atrium cor triatriatum or stenosis of the individual pulmonary veins.)

Pulmonary arteriography was performed in an attempt to define the location of the obstructive lesion This study confirmed the presence of a patent ductus arteriosus with a right to-left shunt (Fig 3) The pulmonary transit time was greatly prolonged Ultimately however the pulmonary veins filled and were observed to

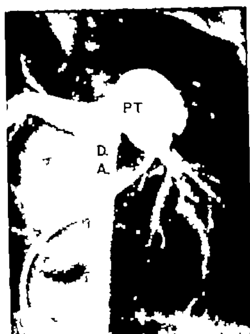


Fig. 3. Pulmonary arteriogram 0.5 second after injection. The pulmonary trunk (*P.T.*) and the descending aorta (*D.A.*) are densely opacified.

connect normally with the left atrium. The veins were not stenotic. The left atrium opacified densely 3 seconds after the injection. In contrast, the left ventricle and aorta did not receive opacified blood until 10 seconds after the injection (Fig. 4*A*). During atrial systole, a conical structure with its apex directed toward the apex of the left ventricle could be clearly delineated (Fig. 4 *B*). Since the left atrial appendage clearly opacified, cor triatriatum (which obstructs the left atrium above the origin of the atrial appendage) could be ruled out. Angiocardiographic findings were thus compatible with congenital stenosis of the mitral valve or supravalvular stenosing ring of the left atrium.

In summary, obstruction existed at or immediately proximal to the mitral valve. The intact atrial septum prevented decompression of the left atrium and resulted in the elevation of the left atrial pressure.

DR. RAO. This infant had significant respiratory distress and did not respond significantly to medical management. Surgical consultation was obtained.

Dr. Castaneda, would you outline the surgical approach devised and describe the operative findings?

DR. ALDO CASTANEDA. Since the obstructing lesion of the left atrium was of major hemodynamic importance, alleviation of this obstruction was our primary goal. It was reasoned that if this were not possible, palliation might be achieved by creating an atrial septal defect, thus decompressing the left atrium. The ventricular septal defect would then allow the return of left atrial blood to the aorta. By relieving the obstruction of the left atrium we anticipated relief from the pulmonary edema and increase in the pulmonary blood flow.

At operation, the thorax was opened through a midline sternotomy. A patent ductus arteriosus was found and it was ligated and divided before placing the patient on cardiopulmonary bypass. On opening the left atrium, we saw a stenotic conelike structure, the base originating from the mitral annulus and the apex extending into the left ventricle. Plastic repair of this valve did not seem feasible. Moreover, the relatively small size of the left ventricle precluded the use of a mitral valve prosthesis.

Therefore, before concluding the cardiopulmonary bypass, a large atrial septal defect was created.

DR. RAO. The patient established spontaneous circulation after discontinuation of the cardiopulmonary bypass. Two hours postoperatively she developed hypotension, hypoxia, and acidosis. Response to treatment with pressor drugs, sodium bicarbonate, and tromethamine (Tham) was poor. Spontaneous respiration could not be maintained and assisted respiration was instituted. Progressive hyperkalemia developed and could not be controlled despite aggressive management. Twenty hours postoperatively, cardiac arrest and death occurred.

Dr. Ibarra, what were the results of the necropsy?

DR. CARLOS IBARRA PEREZ. At necropsy, the great vessels were found to be normally related. The pulmonary trunk and its main branches were dilated. The ductus arteriosus had been ligated and divided. The aortic arch gave off 4 branches in-

nominate left common carotid left and right subclavian arteries in that order from before backward Distal to the left subclavian artery the aorta showed the characteristic deformity of coarctation but the degree of obstruction was minimal.

The circumflex coronary artery arose independently from the right aortic sinus. The venous connections with both atria were normal. The right atrium was dilated The atriale sptum showed a surgically created defect (15 mm in length)

The right ventricle was hypertrophied and dilated the thickness of its wall varied from 4 to 5 mm In the ventricular septum there was an eliptical defect measuring approximately 10 × 15 mm which lay posteroinferior to the crista supraventricularis and was partially obscured by the septal leaflet of the tricuspid valve. When viewed from the left ventricle the defect lay below the posterior half of the left aortic cusp and most of the right cusp No obstruction to left ventricular outflow was identified

The wall of the left atrium was markedly thickened and dilated Its endocardium was thickened varying from 1 5 to 2.5 mm in thickness. The endocardial surface was opaque and ridged the endocardial thickening extended to the orifices of the pulmonary veins but the latter were not noticeably narrowed.

Immediately above the orifice of the mitral valve there was a circumferential ridge of thick opaque, white tissue which formed a narrow eliptical 3 × 1.5 mm orifice at the inlet to the valve (Figs 5 and 6) The ring blended at its base with the thickened endocardium of the atrial wall near the basal attachment of the mitral leaflets. The chordae and papillary muscles of the mitral valve were normal. The mitral leaflets showed minimal fusion at the posterolateral commissure. There was also a polypoid 4 × 3 × 5 mm mass of soft white spongy accessory tissue attached to the atrial surface of the anterior mitral leaflet near the free margin. This tissue prolapsed easily into the left ventricle and may have caused a slight degree of obstruction

On the left side of the ventricular septum beneath the defect, there was a small area of irregularly shaped endocardial thickening this was interpreted as a jet lesion. The thickness of the left ventricular



Fig 4 Pulmonary arteriograms. *A* Atrial diastole 9.5 seconds after the injection. No contrast material present in the left ventricle *B* Subsequent film (10 seconds after the injection) during atrial systole. Opacification of the left ventricle (arrow) is first apparent at this time. The cone-shaped density (arrow) at the base of the left atrium (*LA*) suggests either mitral stenosis or supravalvular stenosing ring of the left atrium Opacification of the left atrial appendage (*LAA*) rules out cor triatriatum

wall varied from 3 to 6 mm. and the cavity was small.

The consistence of the lungs was increased there was conspicuous dilatation of subpleural lymphatics. The tracheobronchial tree contained a large amount of inspissated mucus.

Dr Korns will now describe the histological changes

Dr. Michael E. Korns Half of the thickness of the left atrial wall was accounted for by endocardial fibroelastosis.

A section encompassing a part of the left atrium left ventricle supravalvular ring and posterior mitral leaflet showed in addition to the endocardial fibroelastosis of the left atrium a blunt, shelflike ridge of tissue composed in part of disorganized primitive, mesodermal type tissue (Fig 7) Histologically this tissue which represented the supravalvular ring resembled somewhat the loose connective tissue which comprises the spongiosa of a normal cardiac valve It is noteworthy that the basal attachment of the posterior mitral leaflet and the basal attachment of the supravalvular ring of the left atrium were distinctly separate. The posterior mitral leaflet was somewhat thickened

In the lung the alterations histologically correlated well with the gross abnormalities (Fig 8) There was a moderate degree of dilatation and engorgement of capillaries in the alveolar septa and conspicuous dilatation of the subpleural lymphatics and veins. Similar vessels were also apparent in the interlobular septa. Both large and small tributaries of the pulmonary veins showed varying degrees of medial hypertrophy

Medial hypertrophy of the muscular pulmonary arterioles was uniformly distributed

Dr Edwards will now give a closing summary

Dr. Jesse E. Edwards From the material presented it is clear that the major obstructive lesion was that commonly designated as supravalvular stenosing ring of the left atrium Although this is an uncommon entity it is relatively common among those infants who exhibit obstruction to the flow of blood from the left atrium

Supravalvular stenosing ring of the left atrium may appear either as an isolated anomaly[3] or be part of a developmental complex as described by Shone and as-



Fig 3 A Left atrium (L.A.) from above. The supravalvular ring (between arrows) lies above the mitral orifice and is responsible for zone of stenosis between the left atrium and the mitral valve below Endocardial thickening of the left atrium as well as hypertrophy of the wall are features resulting from the obstructive phenomenon A.S. Site of surgical creation of atrial septal defect. B Opened mitral valve, left atrium (L.A.) and left ventricle (L.V.). Above the mitral valve is protrusion of tissue representing the supravalvular ring (between arrows).



Fig 6 A Left ventricle (L.V.) and unopened mitral valve from below. Beneath the aortic valve is the large ventricular septal defect (D). The probe is in the orifice of the mitral valve. Obscuring a portion of the anterior leaflet is a mass of accessory tissue (A.T.) the basal attachment of which was to the atrial aspect of the leaflet. The posteromedial (P.M.) and the anterolateral (A.L.) papillary muscles are present. B Left ventricle (L.V.) and ascending aorta (A). The ventricular septal defect (D) is large. Through the defect elements of the tricuspid valve may be seen. The mitral valve is out of view in this perspective.



Fig 7 Low power photomicrograph of section through left atrium (L.A.), posterior wall of left ventricle (L.V.), and the posterior mitral leaflet (P.M.). Above the mitral valve is a protrusion of fibrous tissue (R.) representing the supravalvular fibrous ring illustrated grossly in Fig 5. Elastic tissue stain ×7.5

sociates[4] from our institutions. The latter complex is characterized by the presence of 4 obstructive anomalies in the left side of the heart. These are (1) supravalvular stenosing ring, (2) parachute mitral valve, (3) subaortic stenosis, and (4) coarctation of the aorta.

It is of interest that while some patients manifest each of these conditions in a functionally significant state, others exhibit each lesion but only one or several of these are functionally significant. Still other patients show only 2 of the 4 lesions and among these only one may be sufficiently developed as to be functionally significant. It is of interest that in the case presented, 2 of the 4 lesions of the complex described by Shone and associates[4] were present. These were the supravalvular stenosing ring and coarctation of the aorta. The latter lesion was insignificant in degree from a functional viewpoint.

Whether the ventricular septal defect in the case presented should be considered part of the complex under consideration is undetermined. It is of interest that in 2 of Shone's 8 cases a ventricular septal defect was present and in a third case there was a left ventricular-right atrial communication.



Fig. 4 Photomicrographs of the lung *A* Numerous dilated lymphatics are present in the visceral pleura (upper part of illustration) and these extend into an interlobular septum of the lung Hematoxylin and eosin ×42 *B*, Interior of the lung Interlobular septa show dilated lymphatics Hematoxylin and eosin ×47 *C* The alveolar septa are thickened by the presence of engorged capillaries. Hematoxylin and eosin ×340. *D* A pulmonary muscular artery showing medial hypertrophy Elastic tissue stain ×240.

Based upon observations made to date we would consider the patent ductus arteriosus to be of incidental coincidence from the developmental viewpoint.

Diagnosis

Supravalvular stenosing ring of left atrium ventricular septal defect, and patent ductus arteriosus.

REFERENCES

1. van der Horst, R. L., and Hastreiter A. R.: Congenital mitral stenosis, Am. J Cardiol. 20 773, 1967
2. Lucas, R. V J Anderson, R. C., Amplatz, K Adams, P J and Edwards, J E. Congenital causes of pulmonary venous obstruction, Pediat. Clin. North America 10 781 1963.
3. Rogers, H. M Waldron, B R., Murphey D F H., and Edwards, J E. Supravalvular stenosing ring of left atrium in association with endocardial sclerosis (endocardial fibroelastosis) and mitral insufficiency Am. Heart J 50 777 1955.
4. Shone, J D Sellers, R. D Anderson, R. C., Adams, P J Lillehei, C. W and Edwards, J E. The developmental complex of parachute mitral valve supravalvular ring of left atrium subaortic stenosis, and coarctation of aorta, Am. J Cardiol. 11 714 1963

Fundamentals of clinical cardiology

Cardiovascular actions of angiotensin in man

R. F. Whelan, M.D., D.Sc., F.R.A.C.P., F.A.A.
G. C. Scroop, M.D.
J. A. Walsh, M.B., B.S.
Adelaide, Australia

Seventy years ago Tigerstedt and Bergman observed that the injection of a saline extract of fresh rabbit kidney into normal rabbits caused a rise in arterial blood pressure. The renal pressor agent renin has since been shown to be a protein enzyme to come from the juxtaglomerular apparatus and to exert its effect by reacting with its substrate angiotensinogen (a plasma α_2-globulin) to form the octapeptide, angiotensin, which is the active vasoconstrictor principle.

Some of the earliest investigations into the cardiovascular actions of angiotensin in man were performed by Battro and associates[2,3] who observed a rise in systolic and diastolic blood pressure and an accompanying reflex bradycardia mediated by the vagus. Corcoran and associates[4] demonstrated a rise in blood pressure and a fall in renal blood flow, the latter resulting from an action on the efferent arteriole. In addition to increased mean arterial pressure and pulse pressure, Wilkins and Duncan[5] reported an initial increase followed by a fall in forearm and calf blood flow and a fall in skin temperature of the fingers and toes during intravenous administration of angiotensin. There was a rise in central venous pressure and a slight fall in cardiac output. The bradycardia that appeared during the pressor response was not only abolished by atropine, but was often reversed to a slight tachycardia.

Similar changes in cardiac output and blood pressure during intravenous administration of angiotensin in man were observed by other workers.[6-8] There was general agreement that angiotensin elevated the mean arterial blood pressure, an effect that was not modified by spinal anesthesia in man or animals[9] or dibenamine pretreatment in dogs,[10] and was therefore thought to be the result of an overall increase in peripheral vascular resistance mediated by a direct vasoconstrictor action on specific nonadrenergic receptors.

More recent studies in animals, however, have indicated that in addition to a direct constrictor action on the arteriolar smooth muscle, angiotensin has other indirect actions which might contribute to its pressor activity.

Fig. 1 is a diagrammatic representation of the renin angiotensin system with emphasis on the components of the vasoconstrictor action which have been deduced as a result of animal studies. It is the purpose of this article to consider the mechanisms of the vasoconstrictor action of angiotensin and the extent to which these may apply in man. The role of aldosterone release is

From the Department of Human Physiology and Pharmacology, University of Adelaide, Adelaide, South Australia.
Supported by grants from the National Health and Medical Research Council of Australia and the Medical Research Committee of the University of Adelaide.

FALL IN SYSTEMIC OR RENAL ARTERIAL PRESSURE
FALL IN CENTRAL VENOUS PRESSURE
+
+
−
−
RENIN RELEASE FROM AFFERENT ARTERIOLE CELLS
ANGIOTENSIN II
ANGIOTENSIN I
alpha2 GLOBULIN
VASOCONSTRICTOR ACTIONS
ALDOSTERONE RELEASE ★
RENAL TUBULE CELLS
CENTRAL SYMPATHETIC STIMULATION ★
PERIPHERAL SYMPATHETIC STIMULATION
ADRENAL RELEASE OF CATECHOLAMINES
DIRECT ACTION ON VESSELS ★
POTENTIATION OF RELEASED NORADRENALINE ★
SODIUM & WATER RETENTION
INCREASE IN VASCULAR RESISTANCE
INCREASE IN C.B.V.
INCREASE IN M.A.P.

Fig. 1. A diagrammatic representation of the renin-angiotensin system with emphasis on the components of the vasoconstrictor action. Those mechanisms of action for which there is evidence in man are indicated by a star. C.B.V. Circulating blood volume. M.A.P. mean arterial pressure.

the pressor action of angiotensin will not be considered

Direct vasoconstrictor action

Administration of angiotensin into the supplying artery has been shown to result in reduction of blood flow in the forearm calf and hand [4,11,12] In Fig 2 are illustrated the responses of the hand blood flow measured by venous occlusion plethysmography to intra-arterial angiotensin and noradrenaline before (○) and after (●) administration of phenoxybenzamine [5] The constrictor response to angiotensin was somewhat slower in onset than that to a corresponding dose of noradrenaline and it took longer to wear off after cessation of the infusion Comparison of dose response curves to the two constrictor agents has shown that on a weight basis noradrenaline is two to three times as potent as angiotensin in constricting the hand vessels, but in the case of the forearm vessels angiotensin was four times more effective than noradrenaline (Fig 3 upper panels) One possible explanation for this difference between forearm and hand responses to angiotensin might be a rapid uptake or inactivation of angiotensin in the blood stream reducing the effective dose of the drug by the time it travelled from the point of infusion at the elbow to the hand vessels, as occurs with bradykinin and acetylcholine [6] However the degree of constriction produced with equal doses of noradrenaline was the same for the two vascular beds whereas with angiotensin similar constrictor responses in the forearm and hand required 25 times the dose in the latter Since the half life of the two agents in the blood stream is similar it seems likely that the forearm vessels have a greater sensitivity to angiotensin than do the hand vessels.

It has yet to be determined whether the fall in forearm flow produced by intra arterial angiotensin is a consequence of constriction of skin or muscle vessels or of both. As the forearm is largely muscle it has been inferred[13] that changes in total forearm blood flow measured plethysmographically are largely representative of changes in muscle flow alone. However studies with noradrenaline [1] adrenaline,[13] and serotonin[19] have shown that the influence exerted by changes in skin blood flow on the total forearm flow pattern depends on the level of skin blood flow at the time of the infusion. If this is high, a marked vasoconstriction can occur and be sufficient to mask completely a dilatation in the underlying muscles. Only by assessing skin and muscle flow independently can conclusions about muscle flow be made with accuracy

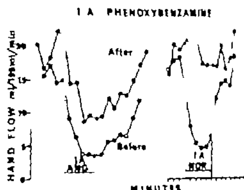


Fig 2 The response of the blood flow through the hand of one subject to intra-arterial angiotensin (0 9 µg per minute) and noradrenaline (0.3 µg per minute) before (○) and after (●) introduction of phenoxybenzamine (1.5 mg in 3 minutes) into the brachial artery of the same arm. (From Scroop and Whelan Clin. Sc 30 79 1966)

Blockade of the alpha-adrenergic receptors of the hand vessels by phenoxybenzamine abolished the response to noradrenaline but left that to angiotensin unaltered (Fig 2) This observation indicated that the direct action of angiotensin was not due to an effect on the α-adrenergic receptors either directly or by way of stimulation of the peripheral sympathetic nerve endings. Further support for the latter conclusion comes from studies on the hand vessels of patients who were suffering from autonomic degeneration or who had undergone surgical cervical sympathectomy (Fig 4) With the exception of Patient W W in whom the responses to both angiotensin and noradrenaline were greater than normal sympathetic denervation had no appreciable effect on the response of the hand vessels to intra-arterial angiotensin. The responses to noradrenaline however showed an increase above normal in most patients

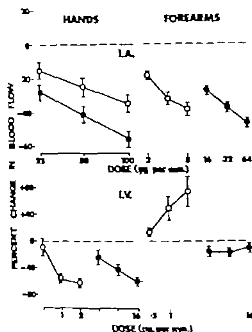


Fig. 3. The mean percentage changes in hand blood flow (left-hand frames) and forearm blood flow (right-hand frames) during intra-arterial (upper frames) and intravenous (lower frames) infusions of angiotensin (O) and noradrenaline ( ) in the doses indicated. The intra-arterial results were obtained from five subjects (each point for the hands representing the mean of eight values in the case of angiotensin and nine in the case of noradrenaline, and for the forearms each point represents ten values, two from each subject). The intravenous results were obtained from seven subjects (each point representing the mean of one value from each subject). The vertical line through each point represents one standard error on either side of the mean. (From Scroop, Walsh, and Whelan: Clin. Sc. 29:315, 1965.)

at all dose levels. The hand vessel responses to angiotensin in Patient R. T. who was studied before and after sympathectomy were not appreciably altered by the operation although the noradrenaline responses were slightly enhanced.

It is concluded that, given intra-arterially, angiotensin has a direct action on the smooth muscle of the blood vessels of the human forearm and hand which is not due to stimulation of the α-adrenergic receptors either directly or indirectly by stimulation of the sympathetic nerve fibers. This is in contrast to findings in animal preparations which indicate that angiotensin releases noradrenaline from the peripheral sympathetic nerve fibers,[22,23] but the concentrations used were very much higher than have been given in human studies.

Central action

Studies on animals have indicated that angiotensin when given intravenously may have indirectly mediated vasoconstrictor actions which could contribute to its pressor effect. Bickerton and Buckley[24] found that when angiotensin was infused into the cerebral circulation of a dog, where the only connection between the head and the body was through the nerves, there occurred a rise in systemic arterial pressure which could largely be prevented by prior treatment of the body with an α-adrenergic blocking drug. The doses used were very large in comparison with those which can safely be given to conscious human subjects and the relative effects of the direct and the nervously mediated constrictor actions in different vascular beds were not determined.

Laverty also found evidence for a nervously mediated component to angiotensin's action on the vessels of the hind limb of the rat. Nishith and associates[26] suggested that, in the dog, angiotensin may have a cardiac accelerator effect exerted through the efferent nerves to the heart. This action is considered to be postganglionic in site and is abolished by bretylium and α adrenergic receptor blockade.[26]

A comparison in man of the actions of intravenous angiotensin and noradrenaline on the cardiovascular system led to the conclusion that angiotensin exerted indirect vasoconstrictor and cardioaccelerator actions,[27] and it has subsequently been demonstrated that at least the vasoconstrictor action in the hands and feet is dependent upon the sympathetic nerves.[4,28]

Blood pressure and heart rate in man. When the effects of doses of intravenous angiotensin and noradrenaline, which produced equal increases in systolic blood pressure, were compared (Fig. 5) it was found that the diastolic pressure always rose more quickly and to a higher level with

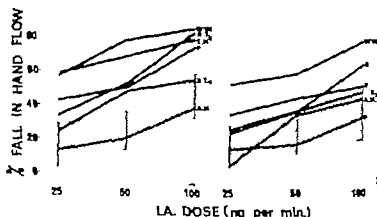


Fig 4 The hatched areas in both frames include one standard deviation about the mean constrictor response of the hand vessels for each of the three doses of noradrenaline (left hand frame) and angiotensin (right hand frame), when administered intra-arterially to five normal subjects. The superimposed dose-response curves (———) were obtained from three patients with autonomic nervous system degeneration (A. H., E. H and P B) and two patients with cervical sympathectomy Patient R T was studied before (R T) and after (R. T) sympathectomy (From Scroop.[16])

angiotensin and the rise in mean pressure was therefore correspondingly greater The heart rate was reduced during infusions of both drugs, but for similar increases in systolic or mean pressure the effect was greater with noradrenaline. In the case of noradrenaline there was a close relationship between the fall in heart rate and the rise in blood pressure but no such relationship was found with angiotensin where the bradycardia did not increase significantly with the increase in pressor effect (Fig 6)

The bradycardia seen with noradrenaline can be attributed to a reflex vagal effect[21,22] initiated by the rise in arterial pressure. That produced by angiotensin is also probably vagal in origin[3] but the fact that it is less marked than with noradrenaline when given in approximately equipressor doses suggested that angiotensin had a stimulating action on the heart which opposed the reflex slowing Such a stimulating action was unlikely to be a direct effect of the drug since a positive chronotropic effect of angiotensin had not been observed on the heart of the kitten frog dog or cat.[20-22]

An indirect stimulating effect of angiotensin which increased with increasing doses could account for the observation that the bradycardia with angiotensin showed no correlation with the degree of hypertension. The lesser degree of bradycardia with angiotensin could account for the greater rise in diastolic pressure with this drug than with noradrenaline for a given increase in systolic pressure.

The increase in central venous pressure produced by both noradrenaline and angiotensin[17] is probably due to the bradycardia since it is reduced or abolished by atropine[22] and the greater effect of noradrenaline could be related to the more marked bradycardia it produces. It may also be of relevance that angiotensin is not as marked a constrictor of capacitance vessels as is noradrenaline.[21,22]

Hand blood flow Intravenous infusions of a range of doses of angiotensin and noradrenaline showed that angiotensin was between eight and ten times more potent as a constrictor of the hand vessels than was noradrenaline (Fig 3 lower left panel) This ratio of potencies was in marked contrast to that found during intra arterial administration where angiotensin exhibited only one half to one third the constrictor potency of noradrenaline (Fig 3 upper left panel) This discrepancy was accounted for by postulating an indirect constrictor effect of angiotensin when given intravenously which did not occur when it was given intra-arterially

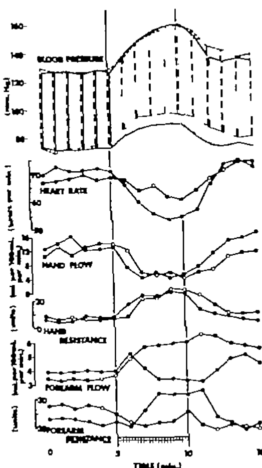


Fig. 5. The changes in blood pressure, heart rate, hand blood flow and resistance, and forearm blood flow and resistance during intravenous infusions of 2.0 μg per minute angiotensin (O) and 16.0 μg per minute noradrenaline ( ), being the averaged data from paired infusions from seven subjects. For each parameter the mean value for the appropriate minute has been calculated and plotted as an individual point. The blood pressure response to angiotensin is indicated by the dotted line and to arterenol by the solid line. The period of infusion is indicated by the hatched area. (From Scroop, Walsh, and Whelan: Clin. Sc. 29:315, 1965.)

The effects of intravenous infusions of angiotensin on the hand treated with adrenergic blocking agents and in sympathectomized, denervated, and nerve-blocked limbs demonstrated that angiotensin has a central sympathetic stimulating action in man and that in the case of the hand vessels the constrictor effect is due entirely to this action of the drug.

The effect of intravenous infusions of angiotensin on the blood flow through both hands was determined before and after treatment of one hand with phenoxybenzamine infused into the brachial artery of that side. Before administration of phenoxybenzamine there was a reduction in blood flow in both hands, the time course and degree of reduction being symmetrical on the two sides. The responses of one hand could therefore be used as a control for the other when this was treated with the blocking drug, the effect of which was confined to that limb and which did not enter the general circulation in sufficient amounts to have any generalized effects. After phenoxybenzamine the constrictor response of the hand vessels to intravenous angiotensin was abolished and the hand vascular resistance increased only slightly while that of the control side was unaffected. Sympathetic reflex responses and the responses to noradrenaline were also abolished or very much reduced on the blocked side, demonstrating the effectiveness of the blocking action of the drug. These observations illustrated the adrenergic nature of the constrictor response of the hand vessels to angiotensin but did not distinguish between sympathetic nerve activity and the arrival of an adrenal hormone since phenoxybenzamine blocks both sympathetic nerve induced activity and also the actions of circulating catecholamines on the hand vessels.

Treatment of the hand with bretylium tosylate, however, indicated that sympathetic nerve activity was involved. The constrictor response of the hand vessels to intravenous angiotensin was very much reduced but not completely abolished, after treatment with bretylium intra-arterially. It was not possible to block sympathetic reflex activity completely with the dose of bretylium used. The slight degree of vasoconstriction and rise in resistance was therefore most probably due to residual sympathetic nerve activity but a contribution to the response by the arrival of adrenal hormones could not be excluded.

However, the results of studies on nerve-blocked, sympathectomized, and denervated limbs demonstrated that the re

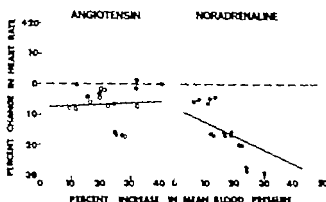


Fig 6 The relationship between percentage change in heart rate and percentage increase in mean blood pressure in several subjects during intravenous infusions of angiotensin (o) in doses ranging from 0.5 to 2.0 μg per minute and noradrenaline ( ) in doses ranging from 2.5 to 16.0 μg per minute. The regression lines for angiotensin ($y = 0.052x - 7.621$) and noradrenaline ($y = -0.449x - 8.02$) are shown. (From Scroop, Walsh, and Whelan Clin Sc 29:315 1965.)

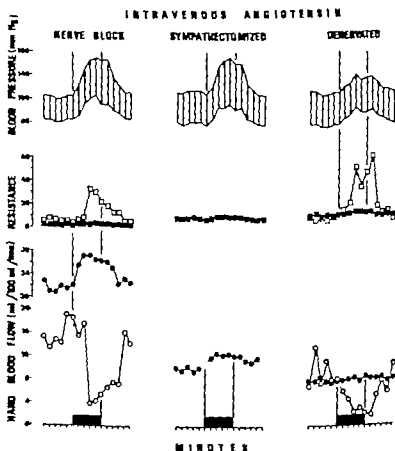


Fig 7 The response of the arterial blood pressure, hand vascular resistance and hand blood flow in control (o) and nerve-blocked sympathectomized and denervated (•) hand of three subjects. Intravenous angiotensin infusions of 2 μg 0.5 μg and 1.5 μg per minute, respectively are indicated by the black rectangles.

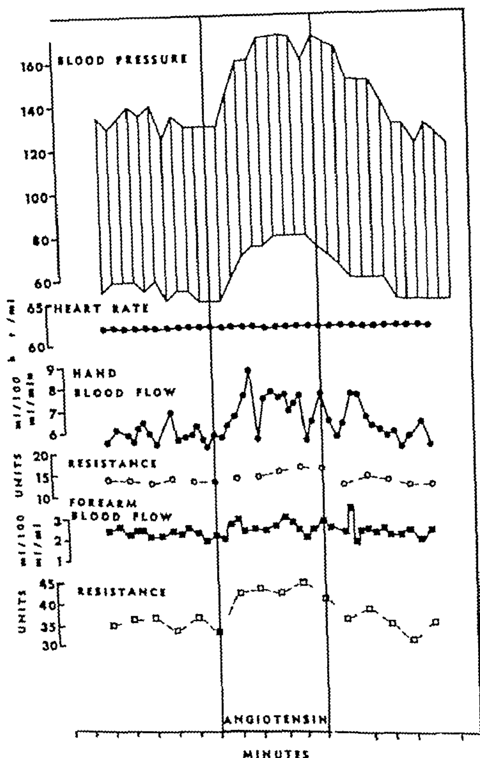


Fig. 4. The effect of intravenous angiotensin (0.25 μg per minute) on blood pressure, heart rate, hand and forearm blood flow, and vascular resistance in a patient with idiopathic autonomic degeneration. (From Whelan, R. F.: Control of the peripheral circulation in man, Springfield, Ill., 1967, Charles C Thomas, Publisher.)

sponse was mediated solely by sympathetic nerves (Fig 7) In none of these did angiotensin have any constrictor effect on the hand vessels A slight increase in flow occurred which was probably a passive response to the rise in blood pressure, since hand vascular resistance showed little change. Constrictor responses to noradrenaline and adrenaline were unimpaired

Similar findings were obtained from studies of a patient suffering from idiopathic autonomic degeneration in whom no sympathetic reflex activity could be demonstrated in the limbs (Fig 8) Hand blood flow rose passively with the increase in blood pressure during angiotensin administration and only a small increase in calculated hand vascular resistance occurred

The blood vessels of the foot behave in a similar fashion to those of the hand.[34] Fig 9 shows the responses of the foot blood flow measured by venous occlusion plethysmography in a patient who had undergone unilateral lumbar sympathectomy three months previously The vessels of the control foot were constricted during intravenous angiotensin but there was no response on the sympathectomized side Before the operation both feet had responded equally to angiotensin.

The small increases in resistance which occurred in the sympathectomized denervated and nerve blocked hands during angiotensin infusions indicated that the vessels were not behaving in a completely passive manner but were probably exhibiting a myogenic response to the increased distending pressure but the action of a circulating constrictor hormone could not be excluded. It is improbable that a direct action of angiotensin on the vessels could be responsible for the slightly raised resistance in the denervated hands in view of the probable concentration of angiotensin calculated to be arriving in the hand during intravenous infusions. The maximum concentration would be 0 2 to 1 0 ng per milliliter if it is assumed that none is destroyed en route and such concentrations would not have any appreciable constrictor action on the hand vessels (Fig 3)

It can be concluded from the above observations that the increase in vascular resistance in the hands and feet during intravenous administration of angiotensin can be attributed to a central action of the angiotensin acting by way of the sympathetic nerves and that a direct local constrictor action of angiotensin does not play any part in the response of these vascular beds. This conclusion is compatible with the observations of Johnson and associates[37] who found that the constrictor effect of angiotensin on hand vessels was inhibited by phenoxybenzamine and guanethidine, and concluded that the constriction was due, at least in part to a central action eliciting increased sympathetic tone.

However a direct effect, either alone or in addition to a sympathetically mediated constriction could occur in other vascular beds, if these were more sensitive to the direct action than are the vessels of the hand and a direct action on other vascular beds must be invoked to explain

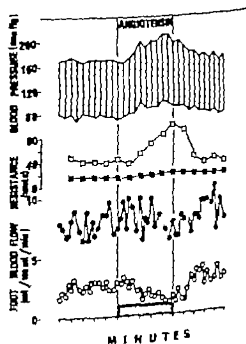


Fig 9 The changes in arterial blood pressure, foot blood flow and foot vascular resistance in the sympathectomized (■) and normally innervated (o) □ feet of Patient D.H. in response to intravenous infusion of angiotensin (1 0 μg per minute — hatched rectangle). (From Scroop.[34])

the pressor response in the absence or blockade of sympathetic innervation. The forearm vessels, for example, are 25 times more responsive than the hand vessels to the direct action of angiotensin (Fig 3) but the forearm vascular bed does not contribute to the increased peripheral resistance during intravenous infusions of angiotensin (see below) The characteristics of other vascular beds have yet to be determined.

The site of the "central" action None of the above experiments provides any information as to the site of the central action of angiotensin which could be either at the sympathetic ganglia or in the vasomotor centers in the brain. A study on one patient, however leads to the conclusion that the site of action is in the centers. The patient had suffered a complete spinal cord transection at the level of the sixth to seventh cervical vertebrae. Angiotensin given intravenously caused a marked increase in arterial blood pressure and a passive increase in hand blood flow calculated hand vascular resistance falling slightly (Fig 10) The responses to noradrenaline were similar to those seen in normal subjects. Since the ganglia and postganglionic pathway were intact in this patient, the absence of the normal constrictor response of the hand vessels indicates that the site of the sympathetic stimulating action of angiotensin is preganglionic.

Forearm blood flow Angiotensin and noradrenaline intravenously had different effects on the forearm blood flow (Fig 3 lower right frame) Noradrenaline caused an initial increase in flow followed by a fall and the forearm vascular resistance rose. During angiotensin infusions the forearm blood flow increased the effect increasing with increasing doses. The calculated forearm resistance, however did not exhibit any significant change.[27] Increases in forearm blood flow have also been observed by others.[4, 22] Bock and associates[11] using calorimetric techniques, found that the blood flow in the muscle of the forearm increased during intravenous angiotensin infusions, while that of the skin decreased This observation has been confirmed using changes in venous oxygen saturation as an index of blood flow Fig 11 shows the changes in arterial pressure, central venous pressure, and muscle blood flow in one subject during intravenous infusion of angiotensin.

Wilkins and Duncan[4] noted an increase, followed by a fall, in forearm and calf flow the increase appearing before the

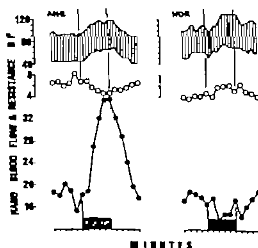


Fig. 10 The response of the arterial blood pressure, hand blood flow ( ), and hand vascular resistance (o) in patient with spinal transection at C6-7 during intravenous infusion (hatched areas) of angiotensin (0 25 μg per minute for 5 minutes, left) and noradrenaline (4 0 μg per minute for 5 minutes, right). (From Scroop.[30])

expected arrival of angiotensin in the part and the appearance and amplitude of the increase were not related to the size of the dose or the degree of increase in arterial pressure In a sympathectomized limb the dilatation was absent and only a constriction was seen It was concluded that the increase in flow was the result of sympathetic motor activity

Similar conclusions can be drawn from the results of the study of a patient suffering from idiopathic autonomic degeneration and in whom no sympathetic reflexes could be induced in the arm or hands with heating or cooling Valsalva's maneuver or postural change and no cardiac reflexes could be elicited Angiotensin caused a marked rise in blood pressure a little greater than normal presumably because of the absence of compensatory baroreceptor reflexes (Fig 8) The forearm blood flow changed little so that the resistance was increased throughout the infusion

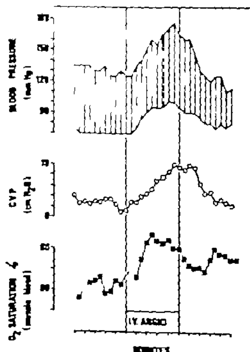


Fig 11 The changes in brachial arterial blood pressure central venous pressure, and deep forearm muscle blood oxygen saturation before, during and after intravenous infusion of angiotensin (2 μg per minute for 5 min tes). (From Mashford Scroop, Walsh, and Whelan, unpublished work.)

whereas the hand flow increased paradoxically and no change in hand vascular resistance occurred

It seems probable that the dilatation of muscle vessels is a sympathetically mediated reflex response to the rise in central venous pressure (Fig 11) Similar responses can be observed in association with alterations in posture when venous pressure changes occur without any change in arterial pressure.[31]

The above findings indicate that, whereas in the case of the hand all of the increase in resistance during intravenous angiotensin is mediated through the central action by way of the sympathetic nerves, in the case of the forearm the flow response is compounded of a direct constrictor action, probably confined to the vessels of the skin and a reflex dilatation of muscle vessels, probably in response to low pressure baroreceptor stimulation. Since the component due to changes in skin flow will vary in magnitude with the state of tone of the skin vessels,[27,31,38] the variability in forearm responses and the apparent discrepancies in the reports of various authors is not surprising

Catecholamine release in man

Feldberg and Lewis[39] injected angiotensin into the renal artery in the cat and demonstrated the release of adrenaline into the venous drainage from the adrenal gland and Peach and co-workers[40] found a dose dependent increase in plasma catecholamine levels during intravenous administration of pressor doses of angiotensin in dogs.

It would appear however that the contribution made by catecholamines released from the adrenal medulla to the cardiovascular action of angiotensin in man is insignificant if indeed it occurs at all.

No change in the urinary vanillylmandelic acid levels followed prolonged intravenous infusions of angiotensin in human subjects.[41]

The fact that sympathectomy nerve block, and denervation did not completely abolish the resistance changes in the hand and foot during intravenous angiotensin infusions (Fig 7) indicated that the vessels

were not behaving in an absolutely passive manner and this might be interpreted to mean that some vasoconstrictor agent such as adrenaline could be circulating. However in the patients suffering from idiopathic autonomic degeneration (Fig 8) and in whom the heart was completely denervated no change in heart rate occurred in response to angiotensin infusion. A tachycardia would have been expected if any significant amounts of catecholamine were being released into the blood stream.

It seems most likely that the slight increases in hand and foot vascular resistance in normal subjects can be attributed to a myogenic response to the increased perfusion pressures.[illegible]

Peripheral sympathetic nerve stimulation

There does not appear to be any evidence in man in support of the possibility that angiotensin might exert some of its constrictor effect by stimulating the release of transmitter from the peripheral nerve endings as occurs, for example, in the case of tyramine.[illegible] If such an effect were present, a constriction of the hand vessels on intravenous administration would be expected in the acutely nerve-blocked limb in which the nerve endings were intact, but no such effect could be detected (Fig. 7). Furthermore the vasoconstrictor action of intra-arterial infusions was not diminished by sympathectomy (Fig 3).

Potentiation of released transmitter

In 1938 Verney and Vogt[illegible] reported an increase in the pressor response to intravenous tyramine in renal hypertensive dogs and Braun-Menendez and associates[illegible] and McCubbin and Page[illegible] observed potentiating interaction between the pressor action of angiotensin and tyramine in the same animal. Zimmerman[illegible] observed that the vasopressor response to angiotensin administered intra-arterially to the perfused dog hindquarters was reduced after acute sympathectomy. Furthermore, the response of the dog cutaneous vessels and the guinea pig vas deferens to sympathetic nerve stimulation has been shown to be enhanced in the presence of angiotensin.[illegible]

Sakurai and Hashimoto[illegible] demonstrated an increase in the response of the vessels of the perfused rabbit ear to noradrenaline and tyramine when administered in combination with subthreshold amounts of angiotensin. The pressor response in the intact rabbit was also enhanced by subpressor amounts of angiotensin.

The possibility that when given in man angiotensin might exert some of its vasoconstrictor action by potentiating the effect of noradrenaline released from the sympathetic nerve ends is supported by two studies on human blood vessels. De la Lande, Frewin and Glover (personal communication) perfused human digital arteries obtained at autopsy with Tyrode's solution at a constant rate and followed the changes in vessel tone in response to added drugs by measuring the accompanying changes in perfusion pressure.[illegible] When a single dose of angiotensin was added to the perfusing fluid it caused a contraction of the vessels. After this had worn off the vessel remained for some time more responsive than before to noradrenaline (Fig 12 upper frame). Likewise when angiotensin was perfused through the vessel in a concentration which was below that required to produce constriction, responses to added noradrenaline were greater than those obtained to the same doses in the absence of angiotensin (Fig 12 lower frame). The increased responsiveness in this preparation was considerable ranging from two to twenty-five fold.

Scroop and Walsh[illegible] studied the interactions between angiotensin, noradrenaline and serotonin on the blood vessels of the human hand and forearm administering the drugs by continuous infusion into the brachial artery at the elbow and following changes in blood flow by venous occlusion plethysmography. They observed that the constrictor action of noradrenaline on the hand vessels was often significantly enhanced in the presence of threshold amounts of angiotensin (Fig 13) but no such potentiation was seen in the case of the forearm vessels. The degree of increase in sensitivity of the hand vessels produced by angiotensin in five experiments on five subjects averaged 35 per cent with a range from 5 to 70 per cent.

The small amount of angiotensin-induced sensitivity in the intact vascular bed of the hand contrasted with the marked potentiation seen in the isolated artery preparation. In explanation of this difference it is suggested that in the case of the isolated vessel the preparation has very little tone and is perfused at a low pressure with an electrolyte solution. It is therefore not exposed to the normal plasma levels of the hormones under study. In the case of the vessels of the intact limb however near maximal interaction may already have been established between the normal levels of noradrenaline and angiotensin and little further potentiation may be attainable by increasing the levels in the perfusing blood by intra arterial administration. It is concluded that, in view of the smallness of the potentiation and the fact that it does not occur in every vascular bed the phenomenon is unlikely to be of biological importance in man.

De la Lande and associates[18] demon-

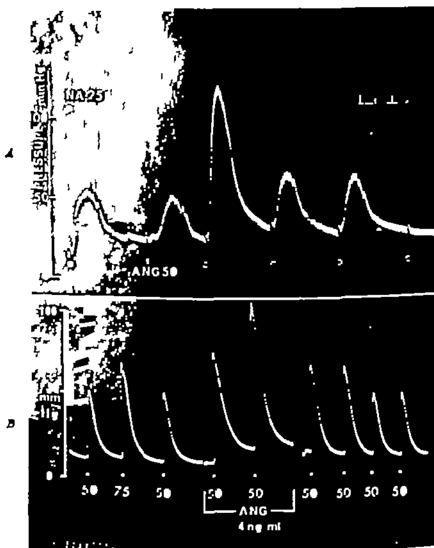


Fig. 12. *A*. The responses of the isolated perfused human digital artery to injections of noradrenaline (0 25 ng) into the perfusion fluid before and after an injection of angiotensin (50 ng). *B*. Responses of the isolated perfused human digital artery to injections of noradrenaline (50 and 75 ng) before during, and after perfusion with angiotensin (4 ng per minute). The time scales of the abscissae are in minutes. (From de la Lande Frewin, and Glover personal communication.)

strated that serotonin potentiated the responses of the isolated rabbit ear artery to noradrenaline and to angiotensin and Scroop and Walsh[58] found this to be the case also for the hand vessels, but not the forearm vessels, in man, using intra-arterial infusions of angiotensin. Serotonin intra-arterially potentiated the effect of noradrenaline on the vessels of the forearm but not on those of the hand

The mechanisms of these various interactions remain to be elucidated

Role of the various constrictor mechanisms in the pressor response to angiotensin

Angiotensin is the most powerful pressor agent so far described Compared to noradrenaline it is six to ten times more active on a weight basis, or fifty to sixty times on a molar basis.[12,37,44] Both agents appear to owe their pressor actions to peripheral vasoconstriction rather than to any significant effect on cardiac output.[17,5] Although a number of vascular beds have

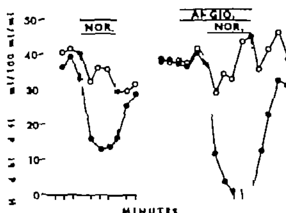


Fig 13. The effect of intra-arterial noradrenaline (400 ng per minute for 4 minutes) on hand blood flow when given by itself (left of figure) and then during the last 4 minutes of an 8 minute intra-arterial infusion of angiotensin (400 ng per minute, right of figure). Infused side o control side. (From Scroop and Walsh Aust. J Exper Biol. M. Sc. 46:573 1968.)

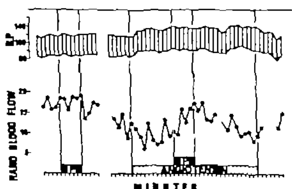


Fig 14 The response of the arterial blood pressure and hand blood flow during intravenous infusion of phentolamine (1 0 mg per minute for 5 minutes) when given alone (left of figure) and when given during an intravenous infusion of angiotensin (1 0 μg per minute for 30 minutes, right of figure). (From Scroop and Whelan Aust. J Exper Biol. M. Sc. 46:563, 1968.)

been studied in man[13] and in animals,[44-48] the site of the major increase in peripheral resistance during angiotensin infusions remains uncertain and the relative roles played by central and peripheral actions on the pressor effect have not been fully evaluated

There is considerable evidence from animal studies, in support of both a pre and a postganglionic sympathetic stimulating action of angiotensin[31 35 53-59] which appears to make a significant contribution to the pressor response [53 54]

However Laurence and Nagle[47] were unable to modify significantly the pressor response in man with either bretylium or guanethidine and some animal studies have led to the conclusion that the sympathetic nervous system does not make a major contribution to the angiotensin pressor response

In a recent endeavor to determine the degree to which the central sympathetic stimulating action of angiotensin might contribute to its pressor effect, angiotensin was given intravenously in normal subjects and the effect of phentolamine on the responses of the blood pressure and hand blood flow determined [71]

The sympathetically mediated constriction of hand vessels which occurred during the angiotensin infusions was abolished by infusion of phentolamine yet the blood pressure increase was not significantly modified (Fig 14) and this was so in all of six subjects studied Although it is unlikely that the alpha receptor blockade was absolutely complete nevertheless, some modification of the angiotensin pressor response might have been expected if sympathetic nerve stimulation was involved in the pressor response It would appear that the sympathetic stimulating action as seen in the vascular beds of the hand and foot where it is responsible for virtually all the vasoconstriction is not sufficiently widespread or is not of sufficient magnitude to contribute significantly to the pressor effect of angiotensin This conclusion is supported by the observation that intravenous angiotensin caused a rise in blood pressure in a patient suffering from idiopathic autonomic degeneration (Fig 9) and in another who was quadriplegic as a result of a spinal cord transection at the level of the sixth to seventh cervical vertebrae (Fig 10)

The failure of phentolamine to modify the pressor response to angiotensin also indicates that adrenal medullary release of catecholamines by angiotensin does not make an important contribution to the pressor response in man This is contrary to the findings in animals, but may reflect species differences or differences in experimental design

In the above experiments in man the doses of angiotensin administered were necessarily smaller than those usually given in animals and the duration of the infusions was short. It may be that with larger doses and prolonged administration the indirect actions of angiotensin would play a larger role in its pressor effect. The degree of adrenal medullary stimulation in both the dog and cat appears to be dose-dependent,[73 44] and there is some evidence to suggest that with prolonged intravenous infusions of angiotensin the initial pressure rise is due to a direct action on the blood vessels but that this is subsequently replaced by an indirect sympathetic mechanism which maintains the elevation of the arterial pressure.[73 77] This evidence is supported by the experiments of McCubbin and associates[78] in which a hypertensive effect of angiotensin in doses which were initially subpressor appeared after several days of continuous infusion in the dog It has been suggested that in renal hypertension the initial mechanism is a humoral one (renin-angiotensin-aldosterone) and unmodified by various forms of sympathectomy whereas in the chronic state a major part of the elevation in pressure appears to be through a neurogenic mechanism.[61 78 79]

In this regard it is of interest that a fall in blood pressure was produced by phentolamine in a patient who suffered from hypertension as a result of renal artery thrombosis and who had very high plasma renin levels and presumably a high level of circulating angiotensin [80] It is possible that with very high blood levels and with a prolonged duration a neurogenic effect of angiotensin had become manifest which was not seen in normal subjects with short infusions of relatively low dosage Further

understanding of the role of the sympathetic nervous system in renal hypertension is of importance in determining the use of antihypertensive agents in the management of this condition.

Sensitivity to angiotensin in hypertension

Kaplan and Silah[84] have shown that the blood pressure response to intravenous angiotensin is less marked in patients with renovascular hypertension than in those with hypertension of nonrenal origin. This difference in reactivity is attributed to the elevated levels of angiotensin in the blood of the former patients.[85, 86] A recent study of the responses of the vessels of the hands to intra-arterial administration of angiotensin in normal subjects and patients with essential, malignant, and renovascular hypertension[87] indicates that the altered reactivity resides, at least in part, in the peripheral vessels. Angiotensin and noradrenaline were infused into the brachial artery at the elbow to avoid systemic effects and the reactivity of the hand vessels determined plethysmographically, the blood flow through the opposite hand being used as a control.

The responses to angiotensin in nineteen patients with primary hypertension and with normal plasma renin levels did not differ significantly from those of normal subjects, which is in accord with the findings of others.[87]

In contrast, three patients who were suffering from renovascular hypertension and who had high plasma renin levels showed a very marked reduction in responsiveness of the hand vessels to angiotensin over a wide range of doses, whereas the sensitivity to noradrenaline was within the normal limits (Fig. 15). One of these patients had unilateral renal artery thrombosis, and one week after removal of the affected kidney, when the blood pressure and plasma renin activity had returned to normal, the hand vascular responses to angiotensin had also returned to lie within the normal range.

One of the patients studied had malignant hypertension, and although the plasma renin level was elevated, the hand vessel responses to both noradrenaline and angiotensin were within the normal range (Fig. 15).

The changed sensitivity of the peripheral vessels to angiotensin has proved of diagnostic value in patients with hypertension in a similar way to the angiotensin pressor test of Kaplan and Silah.[84]

The mechanism of the reduced vascular sensitivity to angiotensin in renovascular hypertension has yet to be determined. It may be related to the pharmacological phenomenon of tachyphylaxis[17] which is

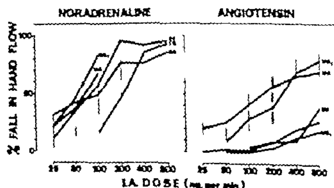


Fig. 15. The hatched areas in both frames include one standard deviation about the mean responses for each of the 6 doses of noradrenaline and angiotensin administered to 5 normotensive subjects. The superimposed dose response curves shown (heavy lines) were constructed from the values for the mean percentage fall in hand blood flow in response to intra-arterial infusion of noradrenaline (left-hand frame) and angiotensin (right-hand frame) in the doses shown. The curves were obtained from one patient with malignant hypertension (M.S.) and three patients with renovascular hypertension (M.O., R.F., and F.M.). Patient M.O. was studied before (M.O.) and after (M.O.) removal of the affected kidney. (From Scroop and Whelan.[87])

seen with a number of drugs in animals and isolated preparations.

Tigerstedt and Bergman[1] reported that on repeated intravenous injection of renal extract in the rabbit the pressor response became less pronounced and Page and Helmer found the same to be true for angiotensin. Bock and Gross demonstrated tachyphylaxis of the blood pressure response to both renin and angiotensin in dogs provided that sufficiently high doses were given and Haas and Goldblatt observed that a state refractory to single intravenous injections of renin and of angiotensin was induced by infusion of renin into the same animal.

Tachyphylaxis to angiotensin has been demonstrated in the isolated rabbit heart, superior cervical ganglion of the cat, guinea pig vas deferens, adrenal medulla of the cat, isolated dog coronary arteries and human umbilical arteries. Khairallah and co-workers investigated the phenomenon in isolated carotid arteries and attributed the tachyphylaxis to saturation of the receptor sites by the infused angiotensin. There are conflicting reports as to whether or not the phenomenon of tachyphylaxis to angiotensin occurs in man. It has been reported[6] that human renal blood flow tends to return to the preinfusion level during angiotensin administration but others have found that prolonged infusions of angiotensin in man did not result in a diminution in the renal blood flow or the pressor response.[7, 8]

Further studies are required before the importance of the phenomenon of tachyphylaxis to angiotensin can be assessed in man.

Summary

Angiotensin exerts a direct action on the smooth muscle of the blood vessels of the human hand and forearm, the latter being the more sensitive.

In addition angiotensin has a central sympathetic stimulating action which, in the case of the hands and feet, is responsible for all of the vasoconstriction seen on intravenous administration.

The central action does not play a significant part in the pressor effect of angiotensin given intravenously for short periods of time.

In contrast to observations in animals, angiotensin in man does not appear to cause release of adrenal medullary hormones, nor does it act on the peripheral sympathetic nerve endings to discharge the transmitter.

Angiotensin causes a modest potentiation of the response of the hand vessels to intra-arterial noradrenaline, which is, however, much less marked than that seen with the isolated perfused digital artery.

The blood vessels of the hands of patients with renovascular hypertension show a very marked reduction in sensitivity to angiotensin, whereas the sensitivity in patients with essential hypertension is within the normal range.

The phenomenon of tachyphylaxis to angiotensin is widely recognized in animals and isolated preparations, but its occurrence or significance has not been investigated in man.

We are indebted to our colleagues, students, and patients who volunteered as subjects for these studies. Angiotensin was generously supplied by Ciba Co. Ltd. Australia, and noradrenaline by Winthrop Laboratories, Australia.

REFERENCES

1. Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf, Skand. Arch. Physiol. 8:223, 1898.
2. Battro, A., Braun-Menendez, E., Lasari, A., and Leloir, L. F.: Accion presora en el hombre de la renina y de la hypertensina, Rev. Soc. argent. Biol. 16:376, 1940.
3. Battro, A., Gonzalez-Segura, R., and Lasari, A.: La accion de la hipertensina en sujetos normales e hipertensos, Rev. argent. Cardiol. 8:250, 1941.
4. Corcoran, A. C., Kohlstaedt, K. G., and Page, I. H.: Changes of arterial blood pressure and renal haemodynamics by injection of angiotensin in human beings, Proc. Soc. Exper. Biol. 46:244, 1941.
5. Wilkins, R. W., and Duncan, C. N.: The nature of the arterial hypertension produced in normal subjects by administration of angiotensin, J. Clin. Invest. 20:721, 1941.
6. Bradley, S. E., and Parker, B.: The hemodynamic effect of angiotensin in normal man, J. Clin. Invest. 20:715, 1941.
7. Taylor, R. D., and Page, I. H.: The effect of ... pressor kidney extract, angiotonin, ... and tyramine on cardiac output as measured by the ballistocardiograph in hypertensive and normal persons, Am. J. M. Sc. 205:66, 1943.
8. Middleton, S., and Waggers, C. J.: The effects

of renin and angiotonin on cardiac output and total peripheral resistance Am. J Physiol. 141:128, 1944
9 Gregory R., Levine, H., and Lindley E. L. Studies on hypertension III. The site of action of angiotonin: the pressor effects of angiotonin on patients having essential hypertension, and possible relationships to the pathogenesis of essential hypertension Texas Rep. Biol. Med 2:121 1944
10 Youmans, W B and Rankin, V M Effects of dibenamine on cardiovascular actions of epinephrine, acetylcholine, pitressin and angiotensin in unanesthetized dogs, Proc. Soc Exper Biol. 66:241, 1947
11. Bock, K. D Krecke, H J and Kuhn, H M Untersuchungen über die Wirkung von synthetischem Hypertensin II auf Blutdruck, Atmung und Extremitätendurch-Blutung des Menschen, Klin. Wchnschr 36:254, 1958.
12. Daly J J and Duff R S. Direct effects of angiotonin on peripheral vessels of subjects with normal and raised blood pressures, Clin. Sc. 19:457 1960.
13. De Bono, E., Lee, G. de J Mottram E. R., Pickering, G W Brown, J J Keen, H., Peart, W S and Sanderson, P H. The action of angiotensin in man, Clin. Sc. 25 123, 1963.
14 Scroop G. C., and Whelan, R F A central vasomotor action of angiotensin in man, Clin. Sc. 30:79 1966.
15. Sameli, K., and Eakes, T K A. B Bradykinin and cardiovascular system estimation of half life, Am. J Physiol. 203:261 1962.
16 Duff F Greenfield, A. D M Shepherd, J T and Thompson, I D A quantitative study of the responses to acetylcholine and histamine of the blood vessels of the human hand and forearm, J Physiol. 120:160, 1953.
17 Cooper C. J Fewings, J D Hodge R. L., Scroop, G C., and Whelan, R. F The role of skin and muscle vessels in the response of the forearm blood flow to noradrenaline, J Physiol. 173:65, 1964.
18. Skinner S. L., and Whelan, R. F The circulation in forearm skin and muscle during adrenaline infusions, Aust J Exper Biol. M. Sc. 40:163, 1962
19 Whelan, R. F and de la Lande, I S. Action of adrenaline on limb blood vessels, Brit. M B ll. 19 125, 1963
20 Whelan, R. F Control of the peripheral circulation in man, Springfield, Ill., 1967 Charles C Thomas Publisher
21 Detler A., Lishau, H and Wolff H. P Action of angiotensin on sympathetic nerve endings in isolated blood vessels, Nature 207 744, 1965
22. Kran, B., and Kharrallah, P A Angiotensin and norepinephrine efflux, Fed Proc. 27 712 1968.
23 Bickerton, R. K., and Buckley J P Evidence for a central mechanism in angiotensin induced hypertension Proc. Soc Exper Biol. 106:834 1961
24 Laverty R. A nervously-mediated action of angiotensin in anaesthetized rats, J Pharm & Pharmacol. 15:63 1963
25 Nashith, S D Davis, L. D and Youmans, W B Cardiovascular action of angiotensin, Am. J Physiol. 202:237 1962.
26. Krasney J A., Paudler F T Smith, D C., Davis, L. D., and Youmans, W B Mechanisms of cardio-accelerator action of angiotensin, Am. J Physiol. 209:539 1965
27 Scroop, G C., Walsh J A., and Whelan, R. F A comparison of the effects of intra-arterial and intravenous infusions of angiotensin and noradrenaline on the circulation in man, Clin. Sc. 29:315 1965
28. Goldenberg, M Pines, K. L. Baldwin, E. de F Greene, D G and Roh, C E. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension, Am J Med. 5 792, 1948.
29 Segel N Harris, P and Bishop, J M The effects of synthetic hypertensin on the systemic and pulmonary circulations in man, Clin. Sc. 20:49 1960.
30 Koch-Weser J Myocardial actions of angiotensin, Circulation Res. 14:337 1964.
31 Hill, W H. P and Andrus E. C. Effects of renin and of angiotensin and other vasoactive agents on small and large blood vessels in several vascular beds, Circulation 23:239 1940.
32. Lorber V The action of angiotensin on the completely isolated mammalian heart, Am. Heart J 23:37 1942
33 Bock, K. D and Gross, F Renin and angiotensin tachyphylaxis, Circulation Res. 9:1044 1961
34 Folkow B., Johansson, B., and Mellander S. The comparative effects of angiotensin and noradrenaline on consecutive vascular sections, Acta physiol. scandinav 51:69 1961.
35 De Pasquale N P and Burch, G E. Effect of angiotensin II on the intact forearm veins of man, Circulation Res. 13:239 1963.
36 Scroop, G C An investigation of the cardiovascular action of angiotensin in man, M.D Thesis, University of Adelaide, 1967
37 Johnsson, G., Henning, M and Åblad, B Studies on the mechanism of the vasoconstrictor effect of angiotensin II in man, Lif Sc 4 1549 1965
38 Roddie, I C., Shepherd, J T and Whelan, R. F Reflex changes in vasoconstrictor tone in human skeletal muscle in response to stimulation of receptors in a low-pressure area of the intrathoracic vascular bed, J Physiol. 139:369 1957
39 Feldberg, W and Lewis, G. P The action of peptides on the adrenal medulla Release of adrenaline by bradykinin and angiotensin, J Physiol. 171:98, 1964.
40 Peach, M J Cline, W H., and Watts, D T: Release of adrenal catecholamines by angiotensin II Circulation Res. 19:571 1966.
41 Vincent, W A., Kashemsant, U Coddy R. P Fried, A. H., Smulyan, H and Elch R. H. Vanillylmandelic acid excretion in labile hypertensive subjects it variation and response to

norepinephrine and angiotensin infusion, Am. J. M. Sc. 219:79, 1965

42. Bayliss, W. M.: On the local reaction of the arterial wall to changes of internal pressure, J. Physiol. 28:220, 1902.

43. Folkow, B.: Autoregulation in muscle and skin, Circulation Res. 14-15 (Suppl. 1): 19, 1964.

44. Frewin, D. B., and Whelan, R. F.: The mechanism of action of tyramine on the blood vessels of the forearm in man, Brit. J. Pharmacol. 33:105, 1968.

45. Verney, E. B., and Vogt, M.: An experimental investigation into hypertension of renal origin, with some observations on convulsive uraemia, Quart. J. Exper. Physiol. 28:253, 1938.

46. Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., and Munoz, J. M.: La substancia hipertensoria de la sangre del rinon isquemiado, Rev. Soc. Argent. Biol. 15:420, 1939.

47. Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., and Munoz, J. M.: Farmacologia de la hipertensina, Rev. Soc. Argent. Biol. 16:398, 1940.

48. Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., Munoz, J. M., and Taquini, A. C.: *In* Renal hypertension, trans. L. Dexter, Springfield, Ill., 1946, Charles C Thomas, Publisher, p. 150.

49. McCubbin, J. W., and Page, I. H.: Neurogenic component of chronic renal hypertension, Science 139:210, 1963.

50. Zimmerman, B. G.: Effect of acute sympathectomy on responses to angiotensin and norepinephrine, Circulation Res. 11:780, 1962.

51. Zimmerman, B. G., and Gomez, J.: Increased response to sympathetic stimulation in the cutaneous vasculature in presence of angiotensin, Int. J. Neuropharmacol. 4:185, 1965.

52. Benelli, C., Della Bella, D., and Gandini, A.: Angiotensin and peripheral sympathetic nerve activity, Brit. J. Pharmacol. 22:211, 1964.

53. Sakurai, T., and Hashimoto, Y.: The vasoconstrictor action of angiotensin in relation to catecholamines, Jap. J. Pharmacol. 15:223, 1965.

54. De la Lande, I. S., and Rand, M. J.: A simple isolated nerve-blood vessel preparation, Aust. J. Exper. Biol. M. Sc. 43:639, 1965.

55. Scroop, G. C., and Walsh, J. A.: Interactions between angiotensin, noradrenaline and serotonin on the peripheral blood vessels in man, Aust. J. Exper. Biol. M. Sc. 46:573, 1968.

56. De la Lande, I. S., Cannell, V. A., and Waterson, J. G.: The interactions of serotonin and noradrenaline on the perfused artery, Brit. J. Pharmacol. 28:255, 1966.

57. Finnerty, F. A., Massaro, G. de C., Chupkovich, V., and Tuckman, J.: Evaluation of the pressor, cardiac and renal hemodynamic properties of angiotensin II in man, Circulation Res. 9:256, 1961.

58. McQueen, E. G., and Morrison, R. B. I.: The effect of synthetic angiotensin and noradrenaline on blood pressure and renal function, Brit. Heart J. 23:1, 1961.

59. Cumming, G. R.: Acute hemodynamic effects of angiotensin II, Canad. M. A. J. 88:827, 1963.

60. Barer, G. R.: A comparison of the circulatory effects of angiotensin, vasopressin and adrenaline in the anaesthetized cat, J. Physiol. 156:49, 1961.

61. Mandel, M. J., and Sapirstein, L. A.: Effect of angiotensin on regional blood flow and regional vascular resistance in the rat, Circulation Res. 10:807, 1962.

62. Haddy, F. J., Molnar, J. I., Borden, C. W., and Texter, E. C.: Comparison of direct effects of angiotensin and other vasoactive agents on small and large blood vessels in several vascular beds, Circulation 25:239, 1962.

63. McGiff, J. C., and Fasy, T. M.: Blockade of the renal vascular activity of angiotensin, Circulation 30:124, 1964.

64. Lewis, G. P., and Reit, E.: Stimulation of the superior cervical ganglion of the cat by angiotensin and bradykinin, J. Physiol. 179:538, 1965.

65. Liebau, H., Distler, A., and Wolff, H. P.: Untersuchungen zur indirekten sympathomimetischen Wirkung von Angiotensin an isolierten Blutgefäßen, Klin. Wchnschr. 44:322, 1966.

66. Halliday, R. P., and Buckley, J. P.: Central hypertensive effects of angiotensin II, Internat. J. Neuropharmacol. 1:43, 1962.

67. Laurence, D. R., and Nagle, R. E.: The effects of bretylium and guanethidine on the pressor responses to noradrenaline and angiotensin, Brit. J. Pharmacol. 21:403, 1963.

68. McCubbin, J. W., and Page, I. H.: Renal pressor system and neurogenic control of arterial pressure, Circulation Res. 12:553, 1963.

69. Gross, M., Montague, D., Rosas, R., and Bohr, D. F.: Cardiac action of vasoactive polypeptides in the rat. II. Angiotensin, Circulation Res. 16:150, 1965.

70. Merrill, A., Williams, R. H., and Harrison, T. R.: The site of action of the renal pressor substance, Am. J. M. Sc. 196:18, 1938.

71. Scroop, G. E., and Whelan, R. F.: The effects of alpha-adrenergic receptor blockade and sympathetic denervation on the pressor action of angiotensin in man, Aust. J. Exper. Biol. M. Sc. 46:563, 1968.

72. Lewis, G. P.: A comparison of angiotensin and bradykinin, Canad. M. A. J. 90:302, 1964.

73. Hill, J. R., and Pickering, G. W.: Hypertension produced in the rabbit by prolonged renin infusion, Clin. Sc. 4:207, 1939.

74. Blacket, R. B., Depoorter, A., Pickering, G. W., Sellers, A. L., and Wilson, G. M.: Hypertension produced in the rabbit by long continued infusions of renin, Clin. Sc. 9:223, 1950.

75. Dickinson, C. J., and Lawrence, J. R.: A slowly developing pressor response to small concentrations of angiotensin, Lancet 2:1354, 1963.

76. Brown, J. J., Chapuis, G., and Robertson, J. I. S.: The effect of prolonged intravenous infusion of angiotensin in the rabbit, Clin. Sc. 26:165, 1964.

77. Yu, R., and Dickinson, C. J.: Neurogenic effects of angiotensin, Lancet 2:1276, 1965.

78. McCubbin, J. W., DeMoura, R. S., Page, I. H.

and Olmsted, F : Arterial hypertension elicited by subpressor amounts of angiotensin, Science 149 1394 1965
79 Reed, R. K., Sapirstein, L. A., Southard F D and Ogden, E.: The effects of nembutal and yohimbine on chronic renal hypertension in the rat, Am J Physiol. 141 707 1944
80 Pickering, G. W Role of the kidney i cute and chronic hypertension following renal artery constriction in the rabbit, Clin Sc. 5:229 1945
81. Taggart, J and Drury D R. The action of renin on rabbits with renal hypertension, J Exper Med. 71:857 1940.
82. Taquini, A C., Blaquier P C., nd Bohr D F Neurogenic factors and angiotensin in the etiology of hypertension, Am. J Physiol. 201 1173 1961
83 Bossin, J M Edwards, R. G Scroop, G C Skinner S. L., nd Whelan, R. F Hyponatraemia and renovascular hypertension. Case report ith plasma renin and vascular reactivity studies, Aust A n. Med in press
84 Kaplan N M and Silah, J G The angiotensin-infusion test, New England J Med 271:536, 1964.
85. Kaplan, N M and Silah, J G Effect of angiotensin II on blood pressure in humans with hypertensive disease, J Clin. Invest 43:659 1964
86 Silah, J G., Strong, C G Nowaczynski, W and Genest, J W The angiotensin infusion test and peripheral venous renin activity Canad M. A. J 96 1397 1967
87 Scroop, G C., and Whelan, R. F Vascular reactivity studies in hypertension, Aust. J Exper Biol. M. Sc. 46:555 1968.
88 Doyle, A. E Fraser J R. E nd Marshall, R. J Reactivity of forearm vessels to vasoconstrictor substances in hypertensive and normotensive subjects, Clin. Sc 18:441 1959
89 Champy C and Cley E. Sur la toxicité des extracts d corps ja ne. Immunisation rapide consécutive à l'injection de petit doses de ces extracts (tachyphylaxie) Soc. Biol. I 159 1911
90. Page, I H and Helmer O M Angiotonin activator renin- nd angiotonin-inhibitor nd the mechanism of ngiotonin tachyphylaxis in normal hypertension and nephrectomized animals, J Exper Med. 71:495 1940.
91 Haas, E and Goldblatt, H Pressor effect of renin, Am. J Physiol 207 1077 1964
92. Beaulnes, A. Effets de l angiotensine sur le coeur Biochem Pharmacol. 12 181 1963
93. Zuberbuhler R C., nd Bohr D F Responses of coronary smooth muscle t catecholamines, Circulation Res. 16:431 1965
94 Davignon J Lorenz, R R and Shepherd, J T Responses of huma umbilical artery t changes transmural pressure, Am J Physiol 209:51 1965
95 Khairallah, P A Page, I H Bumpus, F M nd Turker R K. Angiotensin tachyphylaxis nd ts reversal Circulation Res. 19:247 1966.
96 Bock, K. D and Krecke, H J Die Wirkung von sy thetischem Hypertensin II auf die PAH nd Inulin-clearance, die renale Hamodynamik nd die Diurese beim Menschen, Klin Wchnschr 36:69 1958.
97 Finnerty F A Hemodynamics of angiotensin in man, Circulation 25:255 1962.
98 Laragh J H Cannon, P J Bentzel, C J Sicinski, A. M and Meltzer J I Angiotensin II norepinephrine and renal transport of lectrolytes and water in normal man and in cirrhosis with ascites, J Clin Invest 42 1179 1963.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C. DeGraff, Alan F. Lyon, and Julien Friedman

Treatment of "hypertensive encephalopathy" (accelerated hypertension) Part I*

[illegible] Moser, M.D.**
[illegible] Plains, N. Y.

Urgent treatment of the patient with [illegible] hypertension is extremely important since rapid lowering of blood pressure is often lifesaving. If therapy is initiated prior to the onset of advanced renal failure, blood pressure usually can be reduced, encephalopathy reversed, progressive vascular deterioration halted, and prognosis greatly improved. Since the average age of a patient with this syndrome is 40 to 45 years, reversal of the clinical picture is often a most gratifying experience.

Diagnosis

It is frequently difficult to judge whether a patient is in the "malignant phase" of essential hypertension, has had a temporary "flare-up" of the benign disease with a superimposed anxiety state, or represents an acute case of a collagen disease. As a rough guide, any patient with (1) persistently elevated diastolic blood pressures of 140 mm. Hg or more, (2) left ventricular hypertrophy and/or congestive heart failure, and (3) symptoms of increasingly severe headaches with or without nausea and vomiting, with or without blurred vision or other cerebral symptoms, is in serious difficulty and requires urgent blood pressure lowering regardless of the exact diagnosis. If papilledema and other funduscopic findings are also present, a diagnosis of Grade IV or "malignant" hypertension is made with greater certainty.

Acute glomerulonephritis may produce findings suggestive of the above syndrome, but the history, urinary findings, and generalized edema usually help to differentiate the two entities. Hypertensive encephalopathy is unusual in primary aldosteronism or pheochromocytoma, but the syndrome may occur in patients with renovascular lesions.

Extensive diagnostic procedures may be postponed until the clinical syndrome has been corrected. There is usually time to look for a renovascular lesion, periarteritis, or other disease after treatment. The most important laboratory determination to obtain prior to treatment is the blood urea nitrogen, for therapy may have to be modified if renal failure is present.

Treatment

The patient should be hospitalized and placed on a low sodium diet (1 to 2 Gm. a day). If renal function is poor, a 2 to 4 Gm. a day sodium diet is indicated. If the blood urea nitrogen is normal or only slightly elevated (30 to 35 mg. per cent), the following regime has been found successful.

1. If the patient can tolerate oral ther-

*To be continued. Part II will review additional and new antihypertensive agents as well as the therapy of malignant hypertension with renal insufficiency.

**Physician-in-charge of Hypertensive Section, Montefiore Hospital and Medical Center, New York, N. Y.; teacher in Clinical Medicine, Albert Einstein College of Medicine, New York, N. Y.

apy a thiazide diuretic such as hydrochlorothiazide (HydroDiuril) 50 mg or ethacrynic acid (Edecrin) 50 mg. should be started on a twice-a-day basis. Mecamylamine (Inversine) 5 mg should be given every 2 hours until the blood pressure in the sitting position with legs dangling is between 160/90 and 170/100 Oral mecamylamine is well absorbed and is almost as effective as when administered parenterally It is much safer when given by the oral route

In addition to the above, a Rauwolfia drug (Raudixin 50 mg twice a day) should also be given. It is important to begin all of the drugs simultaneously because few if any patients with accelerated or malignant hypertension will respond to the thiazides and/or Rauwolfia drugs alone, and most will require a potent ganglion or peripheral blocking agent for results. Valuable time is often lost by waiting several days for possible blood pressure lowering effects of the thiazides or Rauwolfia drugs. Permanent organ-system damage (especially renal and cerebral) may occur by the time the more potent drugs are introduced

Mecamylamine is utilized in emergency treatment because of its rapid onset of action (1 to hours) as compared to the delayed blood pressure response to oral guanethidine (Ismelin) (3 to 4 days) The patient is kept in the sitting or semirecumbent position to take advantage of the postural effects of the glanglion blocker Because of the danger of postural syncope the patient should be kept in bed until the dosage of mecamylamine is reduced or the drug stopped (after several days of lowered blood pressure) There is little danger of producing significant ileus or bladder difficulty if dosage is reduced as soon as a blood pressure response is noted.

In most cases, satisfactory blood pressure lowering is obtained on the above program Occasionally a patient will not respond and supplemental parenteral therapy will be necessary If satisfactory blood pressure lowering is not noted after four or five doses of mecamylamine other treatment should be instituted If the patient s clinical condition deteriorates after several hours of oral medication, parenteral therapy should be started immediately

2. If nausea or vomiting is present intramuscular reserpine is indicated When used by the intramuscular route, it is a potent blood pressure-lowering drug which is effective within 1 to 3 hours. Duration of action is between 4 and 12 hours. An initial test dose of 0 25 mg is given intramuscularly since in rare cases, a patient may respond dramatically to a small dose. This is most frequent when the patient has received recent antihypertensive drug therapy especially with the more potent compounds. In such situations, a second test dose of intermediate strength (1 0 mg.) may be given in 2 or 3 hours, or after the initial blood pressure-lowering effect of the first dose has lessened. If a response is not noted following the test dose or doses, 2.5 to 5 0 mg are given every 3 to 6 hours to keep the diastolic blood pressure within an acceptable range of 100 mm Hg or below Reserpine should never be administered on a routine basis every three to four hours. Rather orders should be written if systolic blood pressure rises above 180 to 190 mm Hg systolic, a dose of reserpine should be given intramuscularly (dosage depending upon the amount that had previously been effective) Although the systolic blood pressure may be less important than the diastolic level it is frequently easier for the nursing staff to record accurately and will mirror the diastolic level sufficiently to serve as a guide to drug dosage.

An attempt should be made to wean the patient away from parenteral therapy as rapidly as possible. After three or four doses of intramuscular reserpine, the patient may become depressed or may lapse into a comatose state and present a serious nursing problem If satisfactory lowering of blood pressure is not obtained within 8 to 12 hours, a parenteral ganglion blocker such as pentolinium (Ansolysen) is indicated This drug is not completely absorbed by mouth, but is effective when given intramuscularly on a three to six hour basis or as an intravenous infusion. We prefer pentolinium as the ganglion blocker of choice for parenteral administration since in our experience it is somewhat easier to administer than mecamylamine. The blood pressure should be recorded in the sitting or "dangling position when a ganglion blocker is given parenterally since if taken

when recumbent the blood pressure effect may be missed and excessive dosage given. Blood pressu[illegible] response to intramuscular pentolinium [illegible] 5 to 10 mg.) occurs within 10 to 30 minut[illegible] [illegible]d may persist for 4 to 8 hours. Dosage [illegible]ul[illegible] be titrated to keep the diastolic b[illegible] [illegible]ressure at 90 to 100 mm Hg.

If hospit[illegible] [illegible] are available if they are exper[illegible] [illegible] use of intravenous ganglion bl[illegible] [illegible]ts, and if immediate blood pr[illegible] [illegible]n is deemed necessary (in [illegible] [illegible] edema with high diastolic [illegible] level) pentolinium in doses [illegible] in 300 to 500 c.c. of 5 per[illegible] [illegible] in water may be given intra[illegible] rate of 1 mg. per minute with t[illegible] [illegible] in the sitting position. Great [illegible] [illegible]ul[illegible] be taken to avoid too rapid a[illegible] in blood pressure. When the systoli[illegible] [illegible] pr[illegible] e has dropped to 180 to 19[illegible] [illegible] [illegible] [illegible]nfusion should be discontin[illegible] [illegible] [illegible]lly a further fall in blo[illegible] [illegible] [illegible]thin the next 5 to 10 minu[illegible] [illegible]lly as long as 30 to 45 m[illegible] [illegible] and usually an acceptable le[illegible] of [illegible] [illegible]obtained at that time. If [illegible] the case the infusion may be started [illegible] to accomplish a further drop in blood pressure.

Some patients will respond to as little as 1 to 2 mg. of pentolinium either intravenously or intramuscularly. For this reason careful initial dosage titration is especially important.

If a blood pressure fall results from the above therapy an attempt is made to keep the diastolic blood pressures at 100 mm Hg or less by the use of either intermittent intramuscular reserpine or intramuscular pentolinium until the patient is able to take oral medication. This usually requires 24 to 72 hours of treatment.

The concomitant intravenous administration of 50 mg. of ethacrynic acid will frequently enhance the blood pressure-lowering effect of other parenteral therapy. This dosage may be repeated once or twice daily for one or two days.

When blood pressure has been lowered to acceptable levels, the patient is encouraged to be out of bed as much as possible. Frequently, he is extremely weak, and the process of ambulation may take several to 10 days. A routine is established as quickly as possible so that blood pressure regulation can be attempted with oral medication in an ambulatory individual. Despite this, the drug dosages that are effective in the hospital are often inadequate to control blood pressure when the patient returns to his home or working environment. Blood pressure and drug dosage should therefore be checked within several days and again within two weeks after the patient leaves the hospital.

In general, the patient with an episode of malignant or accelerated hypertension without renal insufficiency can be regulated within a 1 to 2 week period of time and can return to normal activity within 3 to 4 weeks. Most patients with "encephalopathy" or "accelerated" hypertension require at least two or three drugs in combination over a long period of time after they leave the hospital. It is unusual for a patient with hypertension of this severity to respond without the use of hydralazine and/or guanethidine, in addition to a Rauwolfia and diuretic drug. When the acute episode is over, if renal function is not severely impaired, the prognosis of the patient with "accelerated" or "malignant" hypertension is good if therapy is continued and blood pressure controlled.

Annotations

Transseptal catheterization with the aid of a dilating catheter

The speed and ease of advancing a transseptal catheter t the inferior vena cava and right atrium can be enhanced by first using dilating catheter

W make 60 cm. dilating catheter from gray Ödman-Ledin material over a 0 045 inch guide wire and form Cournand bend near the tip. Once the guide wire has been placed percutaneously into the right iliac vein, the dilating catheter is advanced over it to dilate the entrance tract into the femoral vein and to aid in maneuvering the guide wire into the inferior vena cava or the right trium. The dilating catheter is then removed, leaving the guide wire in place, and the transeptal catheter can be easily advanced over the guide wire through the previously dilated entrance tract, thus preserving its tip for transseptal placement, and on to the inferior vena cava and right trium. This also avoids the problems encountered with maneuvering the transseptal catheter with ts oval-type bend through the iliac vein.

R. W yne Neal M.D
Clinical Assistant Professor of Medicine
The University of Oklahoma School of Medicine
Director of Cardiovascular Services
St. John Hospital
1923 S. Utica Ave
Tulsa Okla. 74104

The electrocardiographic ice water test

The exercise tolerance test is the most commonly employed stress test for early recognition of coronary artery disease. However it carries small but definite risk. On exercising patient with suspected coronary disease, one might actually precipitate acute coronary insufficiency or a myocardial infarction. Moreover the interpretation of the exercise tolerance test has been nd still is the subject of much discussion and controversy Unfortunately false-negati nd false-positive responses to exercise continue to present a difficult problem. The lec trocardiographic meal test[1] carries practically no risk it is also less sensitive than the exercise tolerance test. The material is too small to evaluate properly the risk and the sensitivity of the Pitressin test, the Ergonovine test, and the Adrenalin test[2] as compared to the exercise tolerance test. The hypoxemia test[3] carries about the same risk as the exercise tolerance test but is less sensitive.

I the past 15 years, very little study has been done regarding the use of ice water (either by drinking or by immersion) as provocative test for demonstrating myocardial ischemia. I 1923 Wilson and Finch gave 600 c.c. of ice water to 6 normal human subjects and they observed transiently increased negativity of the T wave in Leads II and III Dowling and Hellerstein, in 1951, gave 800 c.c. of ice water to 34 subjects and they found an increase in T wave negativity in Leads II III and V in patients with and without heart disease It has been observed that cooling of the myocardium will result i changes in ventricular repolarization. It may be assumed that the cooling effect on the myocardium may become more prominent and more prolonged in patients with coronary disease in iew of the myocardial ischemia. The purpose of this study is to report our findings in the use of ice water as a means of detecting early coronary artery disease.

A total of 21 normal healthy hospital employees were used as the control group The age range of this group was 21 to 69 years of age. Of this group 5 were men and 16 were women. All of the control group

*Supported in part by National Institutes of Health Grant HE 11233.

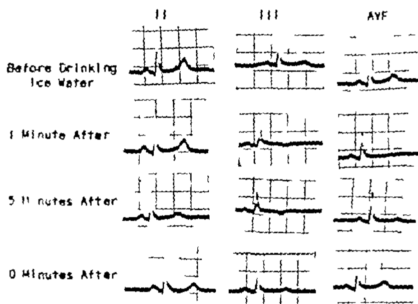


Fig 1 Th ( ] l before nd after ingestion of ice water

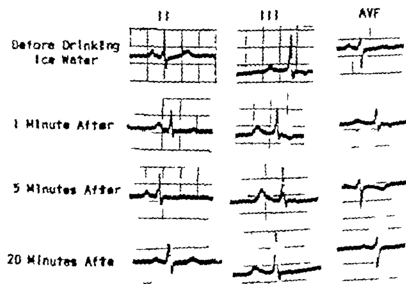


Fig 2 The ECC of patient th known coronary in ufficiency before and after ingestion of ice water

had a history nd ph si l examination which included a chest x y and electrocardiogram (ECG). The history included pecific questions relevant t ny cardiopulmonary mptoma ology The test group included 26 individuals with myocardial infarctions during the pa t 5 years prior t the ice water test. The infarctions were documented by both electrocardiographic and laboratory evidence.

The age group of these 26 individuals with coronary rtery d sease ranged from 51 t 69 years. These indi idual had varying degrees of angina pectoris. All of them however were ambulatory and none of them were in congestive heart failure t the time of the ice water tests. Moreover there had been no sudden increase in their anginal symptoms prior to the taking of the test. Smokers and nonsmokers ere

Table I Decrease of T wave after drinking ice water in 21 normal subjects and 26 patients with coronary heart disease

	Normal subjects (N)			Coronary patients (P)			Difference N P		
Lead	II	III	V	II	III	V	II	III	V
Mean change	−0.19	−1 14	−0.57	−0 44	−0 69	−0 56	−0 25	0.45	0.01
S.D	0 41	0.85	0 60	0.65	0 80	0 74	1 54	1.83	0 07
P (%)	66 4	0.7**	7 8	7.5	0 4**	2.8*	15	6,)	—

Significant (*)approaching significance **highly significant

present in both groups in equal proportion The test consisted of drinking 600 c. of ice w ter with temperature varying between 0 and 2° C. The subject was required to drink this amount of water within period of 3 minutes. (This is the maximum amount of ice ter an individual can tolerate in this period of time) The ingestion of the ice water was done immediately after base-line ECG was taken. An ECG as taken immediately following the ngestion of the ice ater as ell as after 5 10 and 20 minutes (Figs. 1 and 2). The ECG were analyzed and the results tabulated below in Table I

A statistical analysis as made of the changes in the most significa t leads, that is Leads II III and V before and after the ingestion of the ice ater (Table I). These changes were then compared between the normal control group and those changes seen in the test group of coronary artery disease patients. Although the P value in standard limb Lead III of the change in the T wave is highly significant in both the control group and in the coronary artery disease group there was no tatistically significant difference between the T wav changes in the 2 groups

I many of the ndividuals in the coronary disease group ho showed comparatively small changes to the ingestion of ice water further ramifications of the ice water test ere then ndertaken. Eight of the coronary artery disease group had immersion of both hands in ice water as ll as ingestion of the 600 of ice ater The combination of these 2 procedures did not add any significant changes to the electrocardiographic changes noted in Table I Moreover 11 of the patients in the test group were given 100 grams of glucose and after w iting one hour they ere given 600 c.c. of ice water and their hands ere then immersed in ice w ter for 3 minutes The combination of these 3 procedures, i.e., the inges ion of carbohydrate, the ingestion of ice water nd the subsequent immersion of hands in ice water also added no significant change in the ECG Finally 3 of the patients in the coronary disease group ere studied after eating heavy meal and one hour later they ingested 600 c.c. of ice water and their hands ere then immersed in ice ter for period of 3 minutes. ECG t this time did not change significantly from ECG done after the simple ingestion of ice water

I iew of our results, we must conclude that the ice water test is an unsatisfactory method differentiating normals from coronary disease patients.

J fer Knolly M.D
American College of Cardiology Tra nee
Schola at Cardiopulmonary Laboratory
of M Sinai Hospital
Harold Wexler M.D
Clinical I structor
U iversity of Minnesota Medical School
Ernst Simonson M.D
Director Medical-Electronic Research
Professor Emeritus University of Minnesota
Min eapolis Minn

REFERENCES

1 Simonson, E and McKinlay C. A. The meal test in clinical electrocardiograph, Circulation 1 1008, 1950
2 Ruskin, A. Pituitrin test of coronary insufficiency AM. HEART J 34:569 1947
3. Stein, I Observations on the action of Ergonovine on the coronary circulation and its use in the diagnosis of coronary artery insufficiency AM. HEART J 37:36, 1949
4 Levine, S. A. Ernstene, A. C. and Jacobson, B M The use of epinephrine as diagnostic test for angina pectoris, Arch. Int. Med 46 191 1930.
5 Levy R L Patterson J E. Clark, T W and Bruenn, H G. The anoxemia test as an index of the coronary reserve, J A.M.A. 117:2113 1941
6 W lson, F N and Finch, R. The effect of drinking iced ter upon the form of the T deflection of the electrocardiogram, Heart 10:275 1923.
7 Dowling, C. V and Hellerstein, H K. Factors influencing the T ve of the electrocardiogram Effects of drinking iced water AM. HEART J 41:58, 1951

A method for estimation of plasma diphenylhydantoin concentration

Diphenylhydantoin (DPH) is an effective cardiac antiarrhythmic drug. It is particularly useful in the treatment of ventricular arrhythmias. Even though this point is well established, variations occur in the response of individual patients to this drug. One source of this variation is the plasma concentration of DPH, a factor evaluated in a previous study. The results of that study defined the minimal range of plasma levels necessary for antiarrhythmic effect and provided information about the dosage schedules which achieve the effective level. For example, more than 90 per cent of arrhythmias which respond to DPH are abolished at plasma concentrations below 18 μg per milliliter.

Since rapid determination of plasma DPH is not available to the physician during the emergency treatment of cardiac arrhythmias, the purpose of this note is to suggest a means whereby the plasma concentration can be estimated under such circumstances. We proposed that effective plasma concentration be achieved by administration of intermittent small doses in order to avoid undesirable effects of the drug, particularly hypotension. Our usual mode of therapy has been to repeat 100 mg intravenous doses every five minutes. Fig. 1 shows the plasma DPH concentration (μg per milliliter) plotted as a function of cumulative dosage (mg per kilogram) in 12 patients who received the drug by this technique. Plasma samples for determination of drug concentration were obtained just prior to each dose. The black dots represent individual values obtained in these patients. The high cumulative doses and correspondingly high plasma DPH levels in this figure were obtained from patients with ventricular arrhythmias, unresponsive to treatment. The line drawn through the observed points is the calculated regression line for the data. The positive linear correlation between plasma DPH concentration and its cumulative intravenous dose is high ($r = 0.95$, $p < 0.01$). The gray zone represents one standard error of estimate ($S_{y \cdot x}$) about the regression line and is $= 3.3$ μg per milliliter. The plasma level ($\hat{Y}$) estimated on the basis of known cumulative dose can be determined from the formula $\hat{Y} = 2.64 + 2.22X$.

For example, if a patient weighing 79 kilograms with an arrhythmia had been given six 100 mg intravenous doses at five minute intervals, the cumulative dose would be 7.6 mg per kilogram. The estimated plasma DPH level ($\hat{Y}$) would be $2.64 + 2.22 (7.6)$ or 19.4 ± 3.3 ($S_{y \cdot x}$) μg per milliliter. One would, then, know that 68 per cent of patients having received this dose would have plasma DPH concentrations between 16.1 and 22.7 μg per milliliter. Since many patients have central nervous system symptoms when plasma levels exceed 20 μg per milliliter, the presence or absence of such symptoms at this moment could be used as adjunctive evidence. Faced with this situation and armed with the knowledge that 90 per cent of the arrhythmias which will respond to this drug do so below plasma concentration of 18 μg per milliliter, one could decide either to give only one further dose or to discontinue this agent immediately and change to another drug.

The data shown in the figure were gathered under strict conditions of time and dosage. If either variable were altered, the estimation of plasma DPH concentration from this graph should be less accurate. This assumption has been tested and found to be true. If time between doses is lengthened to eight minutes, the plasma concentration at a given cumulative dose is lower. If, on the other hand, the interval between doses (five minutes) is held constant, and the dose changed from 100 mg to 50 mg, the plasma concentration usually rises as a function of cumulative dose in such a way that it remains within the lower limits of the standard error of estimate obtained for 100 mg doses until a cumulative dose of about 5 mg per kilogram is reached. After this level is reached, plasma concentration values consistently fell below the lower limits of $S_{y \cdot x}$.

We have found the relationship shown in the figure very useful in providing a basis upon which to make immediate practical decisions with regard to treatment of arrhythmias with intravenous DPH. Although predictions based on this relationship have usually been borne out when plasma DPH concentration was subsequently measured, the total number of patients studied is too small to assure that the relationship would hold under all conditions.

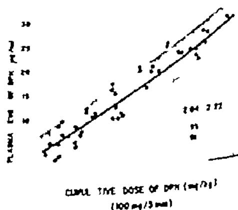


Fig. 1

J Thomas Bigger Jr M.D
Donald H Schmidt M.D
Departments of Medicine and Pharmacology
College of Physicians and Surgeons
Columbia University
630 W 168 St.
New York N Y 10032
Hans Kutt M.D
Department of Neurology in Medicine
Cornell University Medical College
1300 York Ave.
New York N Y 10021

REFERENCES

1. Bigger J T Jr Schmidt, D H and Kutt H. The relationship between plasma level of diphenylhydantoin sodium and its cardiac antiarrhythmic effects, Circulation 38:363 1968.
2. Mercer E. N and Osborne, J A. The current status of diphenylhydantoin in heart disease, Ann. Int. Med. 67 1084 1967

Ventricular fibrillation in acute myocardial infarction: Prognosis following successful resuscitation

Ventricular fibrillation occurring as a complication of acute myocardial infarction is no longer regarded as necessarily fatal, and successful resuscitation with the use of closed chest massage and external defibrillation has become commonplace. Although there has been numerous reports of the incidence of and survival from ventricular fibrillation, little information is available on long-term prognosis.

Table I. Survival following successful resuscitation from primary ventricular fibrillation

Patient	Date of arrest	Known survival	Present state
B L.	February 1963	4½ yr	Alive
J. F	September 1963	1 yr	Unknown
H. W	May 1963	4 yr	Alive
E. F	May 1964	3 yr	Alive
C. C.	September 1964	3 y	Alive
J S.	December 1964	1 yr	Dead
M McD	October 1964	3 yr	Alive
E. M	October 1965	2 yr	Alive
E. R.	January 1966	18 mo	Alive
K. M	January 1966	18 mo	Alive
A. K.	May 1966	18 mo.	Alive
M. S	July 1966	18 mo	Alive
R F	August, 1966	15 mo.	Alive
J R.	August, 1966	1	Alive
J B	August, 1966	1 y	Alive
M. G.	September 1966	1 y	Alive
D B	January 1967	9 mo.	Alive
J T	February 1967	8 mo	Alive
A B	February 1967	6 wk.	Dead
E. S	March 1967	4 mo	Alive

Since the establishment of a Coronary Care Unit at the Royal Melbourne Hospital, 28 of 350 patients suffered primary ventricular fibrillation while in the Unit, and of these nine survived to leave hospital. There were a further eleven survivors from cardiac arrest due to ventricular fibrillation complicating acute myocardial infarction which occurred elsewhere in the hospital who were transferred to the Coronary Care Unit for management following resuscitation.

These 20 surviving patients have now been reviewed (Table I). There were 13 male and 7 female survivors with an age range of 37 years to 68 years, (mean 54.6 years). Eighteen of the 20 patients have survived the longest period of survival being 4½ years. One patient could not be traced at the present time although he is known to have survived for one year. All the men under the age of 65 years are working and the others are leading comfortable lives. None is an invalid.

The two patients who died survived for six weeks and one year respectively before succumbing to further infarction complicated by severe cardiac failure. None of the patients was treated with antiarrhythmic drugs after discharge from hospital. Sudden death which could be attributed to an arrhythmia has not occurred in any patient.

This review indicates that, if a patient survives primary ventricular fibrillation occurring as a complication of acute myocardial infarction, the outlook for long-term survival is good and there seems to be no indication for long term treatment with antiarrhythmic drugs.

Mary Sleeman* M.B., B.S
Graeme Sloman M.B. B.Sc. M.R.C.P
F.R.C.P.(Ed.), F.R.A.C.P
Cardiac Department
Royal Melbourne Hospital
Victoria 3050 Australia

*Supported by Grant-in-Aid G428 from the National Heart Foundation of Australia.

Book reviews

THE AURICULA [illegible] CARDIOGRAM. By Henry A. Zimmerm[illegible] J. Bernano, and Carlos Dicosky. Springfield [illegible] 1968. Charles C Thomas, Publish[illegible] [illegible] 8.00.

This is a [illegible] tle book. It is written in lucid [illegible] manner [illegible] seems to cover [illegible] the [illegible] lar lectro-cardiog[illegible] subject which this [illegible] have been covered profitab[illegible] book devoted t[illegible] such [illegible] include [illegible] comple[illegible] chaotic trial mech[illegible] trial pert[illegible] ard[illegible] d esophageal lec[illegible] trations presented are [illegible] A more complet[illegible] the value of the [illegible] covered is highly re-[illegible] provide of value and [illegible] more than superficial [illegible]

T[illegible] [illegible] HEART DISEASE. [illegible] M.B., and Ali Mehrin, [illegible] W. B. Saunders Com-[illegible]

[illegible] the series on major prob-[illegible] This book is based on [illegible] the [illegible] thors at the Johns Hopkins [illegible] discuss the embryology [illegible] the heart [illegible] fetal and neonate [illegible] of congenital defects, the [illegible] common [illegible] are anomalies of the heart [illegible] ted congenital and hered-[illegible] The text [illegible] clear and well organized. The bibliography is good and the [illegible] All cardiologists, especially pediatric cardiologists, will find the book extremely useful practical and valuable part of personal library.

THE NATIONAL DIET HEART STUDY FINAL REPORT. By the National Diet Heart Study Research Group with the approval of the Executive Committee on Diet and Heart Disease. New York, 1968, The American Heart Association, Inc., 428 pages. Price $3.50.

This is the final report of [illegible] tensive study by an impressively large number of people on the influence of diet on the heart. The physician will find little new from [illegible] practical clinical point of view. He will continue with the same advice on diet to his patient even after [illegible] study of this extensive report. The report clearly displays the many problems encountered in the study of the dietary intake of man. For example the accuracy of measurement of a diet, dropouts, and questions of absolute adherence to the diet are among the many problems offered by the patient. The investigators and their [illegible] also introduce errors in observation and recording of data. The methods of analysis are extremely good but the reviewer is concerned about the reliability of data provided the statisticians. In spite of the tremendous effort and expense involved in this study it is unfortunate that a definite answer on the quantitative role of diet in the production of atherosclerosis and coronary heart disease remains unknown. It is doubtful that physicians in practice will find the monographs to be useful. Nevertheless, it should be available in libraries for reference.

THE HEART AND THE LAW—A PRACTICAL GUIDE TO MEDICOLEGAL CARDIOLOGY. By Elliot L. Sagall, M.D., and Barry C. Reed, LL.B., New York, 1968, The Macmillan Company. 842 pages. Price $25.00.

Physicians and lawyers in general should find this useful book. Although it is concerned primarily with the heart, the principles and problems are common to all medicolegal litigations. The first 300 pages of the discussion are concerned with general aspects of gathering and presenting evidence as well as general principles of litigation. The remaining 500 pages are devoted to problems related to the heart. The authors discuss medical aspects of cardiology for the lawyer and legal principles for the physician in an effort to bridge the gaps in knowledge. This is done very well. Literature is recommended for supplementary reading. A glossary and appendix are also included. Principles for quantitating disability are outlined and included in a chart enclosed in a pocket attached to the back cover. This is a valuable and well-organized useful book, which is recommended to all physicians whether or not they do court work.

ENDOCARDITIS. By Felix Anschütz, Stuttgart, 1968, Georg Thieme Verlag, 264 pages.

This monograph on endocarditis includes etiologic, clinical, pathogenic, pathologic, and therapeutic aspects of endocarditis. The book is well written and nicely supported by tables, charts, and figures of lesions. The chapters of the various contributors are well integrated in subject and style of presentation. Each chapter is appended with a good bibliography and the index is good. The subject is thoroughly discussed in one volume. The book is recommended to all physicians who are confronted with the management of endocarditis. Cardiac surgeons will also find this book to be u[illegible] [illegible] endocarditis following cardiac surge[illegible] [illegible]ted.

AKTUELLE PROBLEME DER VEKTORKARDIOGRAPHIE. By Rudolf Wenger Stuttgart, 1968 Georg Thieme Verlag 398 pages.

Wenger ell know thority on vectorcardiography has edited the proceedings of symposium on vectorcardiography held in Wien, during September 1967 As in all proceedings of international ymposia, the brief summaries of the ork of respective experts in the field are published for the benefit of those wh could not be present Many papers are summarized on electrophysiology methods, clinical diagnosis, and data processing These papers and the interesting discussions are clearly written and illustrated. The publication is excellent and represents good summary of the present status of vector cardiography Everyone in cardiology will find the book, almost entirely in English, to be extremely valuable.

PRACTICAL ELECTROCARDIOGRAPHY By Henry J L. Marriott, M.D Baltimore, 1968, The Williams & Wilkins Company 282 pages. Price $7 75.

The book is now in its fourth edition which reflects its reception and usefulness. A in the other editions, Doctor Marriott has emphasized the practical aspects of electrocardiography It is not an advanced book on the subject or does it include principles in electrophysiology or electrocardiology It is good as book for physicians and beginners. The bibliography includes important references to the literature for more extensive review This is concise, practical book.

BALLISTOCARDIOGRAPHY AND CIRCULATOR FUNCTION Proceedings of the Twelfth Annual Meeting of the Ballistocardiograph Research Society at Atlantic City N J April 29 1967 and report on the activities of the Society edited by William R Scarborough, Basel, 1968, S. Karger AG 171 pages Price $9.35.

This is the publication of the proceedings of the T elfth Annual Meeting of the Ballistocardiograph Research Society held in Atlantic City in April, 1967 The participants represent leaders in the field who discussed many phases of ballistocardiography including technique, frequency characteristics of recorders, hemodynamic relationships to the completed record, quantitative ballistocardiography the H wave, and relationship of the BCG to the age of patients. The publication is elcomed by those of us who were not present at the meetings and is recommended to all ho have interest in BCG.

HEART FAILURE—PATHOPHYSIOLOGICAL AND CLINICAL ASPECTS. By Herbert Reindell, Joseph Keul, and Erich Doll, Stuttgart, 1968, Georg Thieme Verlag 610 pages.

This publication is summary of an international symposium on heart failure held in Hinterzarten during November 1967 The attendance was large and the discussions extensive. Papers by experts in the field are followed by a summary of the discussions. The presentations include selected aspects of hemodynamic changes, the pressure-vol me diagram, biochemistry of the failing heart, electron microscopy of the diseased heart, pathogenesis, clinical manifestations, and many other important problems related to cardiac failure The papers vary in length from a page or two t several pages. The illustrations are good and the text (mostly in German) is concisely written Well-selected references are included. This is very good and useful publication of what must have been an interesting sympos m.

P-Q-R S-T—A GUIDE O ELECTROCARDIOGRAM INTERPRETATION Ed 5 by Joseph E. F Rhseman, M D New York, 1968, The Macmillan Company 321 pages. Price $9 95

This ell-known, practical guide to interpretation of the electrocardiogram is ow in its fifth edition an expression of its reception. Riseman has modified the illustrations and interpretations to maintain an up-to-date guide. The illustrations are clearly presented and the interpretations accurate This book is recommended t all beginners electrocardiography not as substitute for other books on the subject, but as small atlas of representative tracings.

CARDIOVASCULAR DISORDERS Edited by Albert N Brest, M D and John H. Moyer M D Philadelphia, 1968, F A. Davis Company 1 104 pages. Price $24 00

This new textbook, edited by Brest and Moyer is designed like all other books written by many contributors who are leaders in the field concerned The publication is designed as fairly complete textbook on cardiology and the peripheral circulation In fact, the primary criticism may be related to the fact that over 100 people contributed to the book and therefore it may be considered little diffuse with so many contributors. On the other hand, this is good in that the book represents an excellent spectrum of opinions and practices in the management of cardiovascular diseases. The subjects discussed are essentially as expected and the approach conventional. The 89 chapters are lucidly written, the illustrations clear and the bibliography included after each chapter is good This textbook is written for clinicians. It is very good and should be of considerable value to all physicians who treat heart diseases as well as medical students, interns and residents. Like any text book, the subjects discussed are only briefly presented and, of course, cannot be construed to represent complete review of the subject. Nevertheless, this is good textbook.

Announcements

Eleventh Congress of the Pan Pacific Surgical Association will be held October 14 through 22, 1969 (following the meeting of the American College of Surgeons in San Francisco, October 6 through 10, 1969) in Honolulu, Hawaii.

The scientific program will consist of some 350 speakers in 11 surgical specialties. Concurrent meetings will be held in colon and anorectal surgery, general surgery, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedic surgery, otolaryngology, plastic surgery, thoracic-cardiovascular surgery and urology. Included in the program will be meetings in anesthesiology and radiology.

All scientific meetings will be held in the morning leaving afternoons free for sightseeing and social events. It is strongly recommended, therefore, that you bring your family with you to take advantage of this combined scientific meeting and family holiday.

The International Symposium on Pulmonary Circulation sponsored by the European Society for Clinical Physiology of Respiration, will be held in Prague on June 10-13 1969.

For more information write to Czechoslovak Medical Society J. E. Purkyne, International Symposium on Pulmonary Circulation, Sokolská 31, Praha 2 Czechoslovakia.

American Heart Journal

May 1969 Volume 77 Number 5

Editorial

The dilemma of surgery in the treatment of coronary artery disease

*Henry A. Zimmerman, M.D.**
Cleveland, Ohio

Certainly the medical management of coronary artery disease leaves a lot to be desired. However, the surgical management of coronary artery disease is in a state of almost total chaos. The thinking is obviously clouded and total disagreement appears rampant as to supposed methods of revascularization of the myocardium. Patients are led to believe the operation is a curative rather than a questionable palliative measure.

One group of surgeons speaks of the glowing success of the use of internal mammary artery transplants. Another eminent group states they have abandoned its use because of sclerosis in the internal mammary arteries. Others advocate the use of omental grafts while the opposition decries its use, and so on for endarterectomy, vein bypass, venous patching, splenic artery implantation, gastric epiploic implantation, Senn procedure, gas endarterectomy, Dacron prosthesis, poudrage, transplantation, etc.

A group tries to prove the value of their procedure by performing surgery on hundreds of cases. This is taken as positive proof that the procedure works.

At the moment, there are no valid objective studies to show the merit of any of these procedures. No one has documented flows, resistance studies, or perfusion adequacy. Metabolic myocardial studies done in one center cannot be reproduced at another. When lactate production is reduced or abolished, this supposedly proves the improvement of myocardium metabolism by myocardial revascularization. Yet the area producing lactate could now be a fibrous scar with no lactate production, and while the chemistry appears improved, the patient actually has less working myocardium.

Another group has shown hundreds of times a coronary artery cineangiogram showing an implanted internal mammary artery filling the descending coronary artery. For every one case like this, there are hundreds of other cases which show only a small tuft of few vessels arising from the internal mammary, and further, a significant percentage of the transplanted internal mammary arteries are completely blocked when studies are carried out six months to one year later.

To inject a vessel and visualize it is

*Director, Marie L. Coakley Cardiovascular Laboratory, St. Vincent Charity Hospital, Cleveland, Ohio.

certainly not in any stretch of the imagination proof that this vessel is perfusing a portion of the myocardium. Four to 6 c.c. of dye are injected into the vessel in 1 to 1½ seconds at a pressure many times the normal perfusion pressure and flow. On the other hand, one might expect to see diffuse blanching when the involved coronary artery is injected if the flow was significant to the cellular level.

Until such time as reproducible objective studies can be devised to measure flow and area perfusion and the state of the myocardium, the status of all revascularization procedures can be classified as experimental and not proven. Studies must be done of well-documented cases, and twenty cases well studied are far more important than 500 or 1,000 cases haphazardly studied.

It has been suggested that blood supplied to the myocardium by a revascularization procedure might be shunted through an A-V fistula, bypassing the capillary bed entirely.

It must be clearly recognized that the coronary circulation is quite different from the circulation in all other areas of the body and one must take into account the atrioluminal, sinusoidal, thebesian and Wearn vessels and the built-in collateral channels in assessing and devising possible methods of revascularization of the myocardium.

Clinical communications

The effects of sublingual nitroglycerin on myocardial blood flow in patients with coronary artery disease or myocardial hypertrophy

Richard P. Carson, M.D.
William S. Wilson, M.D.
Martin J. Nemiroff, M.D.
William J. Weber, M.D.
Ann Arbor, Mich.

Since the introduction of the organic nitrate compounds, glyceryl trinitrate and amyl nitrate, in the 1860's for the treatment of angina pectoris, they have maintained a dominant position among the group of pharmacologic agents used for the relief of this distressing and serious syndrome. Their proven efficacy has made them the standard by which all other antianginal drugs are judged. Yet despite a century of clinical experience, the mechanism by which they produce their therapeutic response is still unclear. The original rationale for the use of nitrates was derived from the belief that anginal pain was brought about by peripheral vasoconstriction based on clinical observations of changes in peripheral pulses during an attack. Subsequent studies have led to the conclusion, now commonly accepted, that angina pectoris results from myocardial ischemia elicited by a disturbance in the balance between coronary oxygen supply and myocardial oxygen demand. Gorlin and his colleagues have recently documented the occurrence of cardiac ischemia by demonstrating myocardial lactate production during spontaneous angina pectoris. The demonstration of nitrate induced coronary vasodilatation in the revived human heart during Langendorff perfusion, in patients studied by coronary arteriography, as well as in many animal experiments, gives credence to the theory that the nitrates relieve the pain of angina through coronary vasodilatation and consequent improvement in coronary blood flow and myocardial oxygen supply. However the clinical ineffectiveness of several drugs which have been shown experimentally to produce coronary vasodilatation and the failure to detect increases in myocardial blood flow following sublingual administration of ni

From the Departments of Pharmacology and Internal Medicine, The University of Michigan and the Medical Service, Veterans Administration Hospital, Ann Arbor, Mich.
Received for publication July 23, 1968.
Post Doctoral Fellow in investigational clinical pharmacology supported by United States Post Doctoral Training Grant 5T1-HE-5126-04. Present address: U. S. Army Medical Laboratory, Fitzsimons General Hospital, Denver, Colo. 80240.

troglycerin in patients with coronary disease[4, 5] does not substantiate this theory and in fact this evidence can be used to support the assumption made over 100 years ago that the therapeutic effect of the nitrates stems from their peripheral action

Bernstein and associates[6] utilizing the xenon 133 method to measure myocardial blood flow in patients with arteriographically demonstrable coronary artery disease were able to show increases in myocardial flow in these patients following intracoronary injection of nitroglycerin but not after sublingual administration Based on their results they proposed the theory that nitroglycerin exerts a biphasic action consisting of an initial increase in myocardial blood flow subsequent to coronary vasodilatation and reduction in coronary vascular resistance followed by a decrease in myocardial flow as the systemic effects of the drug predominate and arterial pressure falls

Using the same radioactive inert gas method we have been able to observe increases in myocardial blood flow after sublingual administration of nitroglycerin in some patients with coronary disease by obtaining such measurements at a time concomitant with the clinical onset of action and before the systemic effects of the drug have become firmly established

Methods

Nine patients undergoing selective coronary arteriography during cardiac catheterization were studied All subjects were fasting and premedicated with 75 to 100 mg of meperidine HCl and 50 to 100 mg of pentobarbital or secobarbital Coronary artery catheterization was performed via a right brachial arteriotomy utilizing a Sones catheter Proper position of the catheter was confirmed by injection of 1 to 2 ml. of diatrizoate. Myocardial blood flow was measured by the selective injection of xenon 133 in saline into the right coronary artery in all cases and calculated in milliliters per minute per 100 Gm from the rate of precordial disappearance of radioactivity detected by an external scintillation counter as originally described by Ross and associates A five minute interval was allowed between diatrizoate injection and the initial myocardial blood flow measurement

Following two control measurements of myocardial blood flow subjects were given 0 3 mg of nitroglycerin sublingually and xenon 133 injected 90 to 120 seconds later In six of the nine subjects, myocardial blood flow was also measured 5 to 6 minutes after nitroglycerin administration. The coronary catheter was left in place throughout the study to allow rapid repeated measurements of myocardial blood flow and to avoid the necessity for additional injections of contrast medium. No significant obstruction to coronary flow by the catheter could be detected during the procedure. No subject experienced angina or electrocardiographic changes and in three patients no differences between control measurements were observed whether the catheter remained in place or was immediately withdrawn following injection of the xenon 133 solution.

Mercury strain gauge digital plethysmography was utilized to determine the onset of peripheral vasodilatation following nitroglycerin administration This was considered the point at which a sustained increase in pulse amplitude was first observed.

Subjects were separated by clinical and arteriographic criteria into three categories normal those with coronary artery disease and those with myocardial hypertrophy Only one subject (H M) was completely normal from a cardiovascular standpoint. His pain syndrome was not typical of angina pectoris, and physical examination, resting and exercise electrocardiograms, and arteriography were all normal.

Five patients were considered to have coronary artery disease on the basis of abnormal arteriograms and the presence of at least one of the following (1) typical history for angina pectoris (2) positive exercise electrocardiogram and (3) documented history of myocardial infarction.

The remaining three subjects presented with histories of congestive heart failure persistent cardiac enlargement and left ventricular hypertrophy Coronary arteriograms were normal in two of these subjects who were felt to have idiopathic myocardial disease. One of these subjects (P B) had typical anginal episodes re-

lieved by nitroglycerin. The third subject in this group (W. H.) had long-standing rheumatic mitral disease and abnormal arteriograms. However, he had no history of angina or previous myocardial infarction. Exercise electrocardiograms were not performed in these three patients.

Results

The variability in control measurements for these studies was small, averaging ± 3 per cent of the mean control value for each subject. This is probably related to the fact that in most instances the catheter was left in place and not repositioned between measurements. The results are summarized in Table I and presented graphically in Fig. 1.

Group I, normal. The single normal subject showed an initial 14 per cent increase in myocardial flow. This measurement began 102 seconds after drug administration and 29 seconds before an increase in peripheral pulse amplitude was noted. A second measurement taken 370 seconds following drug revealed myocardial flow had fallen to 8 per cent below control values.

Group II, coronary artery disease. Initial measurements of flow in these five patients started an average of 109 seconds after drug and 21 seconds before onset of peripheral vasodilatation. One subject showed no change in myocardial flow, while four showed increases ranging from 3 to 13 per cent. The mean increase for this group was 5 per cent above control. A second measurement was obtained in three of these subjects 320 to 330 seconds following drug administration. Two subjects demonstrated decreases of 10 and 23 per cent below control; the remaining subject showed essentially no change.

Group III, myocardial hypertrophy. Flow measurements in these three subjects were taken an average of 97 seconds after drug and 25 seconds prior to the onset of peripheral pulse changes. Decreases in myocardial flow from 7 to 12 per cent were detected in all three. Repeat measurements were obtained in two of the three subjects 306 to 330 seconds following drug administration and revealed further decreases to 17 and 15 per cent below control levels.

Discussion

The measurement of myocardial blood flow by direct intracoronary injection of solutions of radioactive inert gas is based on the theory that the rate of exchange of an inert gas between tissue and blood is limited by blood flow.[11] Following the injection, coronary arterial blood concentration of the tracer becomes essentially zero and the gas which has been taken up by the myocardium begins to diffuse back

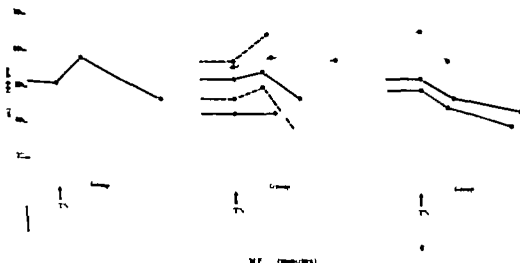


Fig. 1. Effects of sublingual glyceryl trinitrate, 0.3 mg., on myocardial blood flow in man. See text for details.

Table I. Effect of glyceryl trinitrate on myocardial blood flow in man*

Subject	Sex	Age	Group†	MBF (ml./min./100 Gm.)			MBF (% change)§		MBF time‖ (sec.)		Onset peripheral vasodilation (sec.)
				Control‡	Early	Late	Early	Late	Early	Late	
H M	M	31	I	52	59	48	+14	−8	102	370	131
R H	M	42	II	57	59	58	+4	+2	120	330	98
H B	M	36	II	58	65		+13		105		120
H L	M	49	II	44	44		0		130		118
C R	M	48	II	53	55	48	+3	−10	93	320	109
W K	M	46	II	48	51	37	+6	−23	96	330	127
J B	M	43	III	66	58		−12		90		119
L B	M	47	III	50	46	41	−7	−17	95	306	136
W H	M	46	III	53	48	45	−9	−15	105	330	112

*0.3 mg. administered sublingually.
†Group I, normal; group II, coronary artery disease; group III, myocardial hypertrophy.
‡Average of at least two measurements during control period.
§Difference between treatment and control measurements expressed as per cent of average control.
‖Interval from drug administration to start of xenon-133 washout.
Represents single measurement during control period.

into the blood. The exponential rate of washout of myocardial radioactivity is thus theoretically a function of capillary blood flow and is detected by an external counter positioned over the precordium.

Due to the rapid pulmonary excretion of the gas and because satisfactory time-concentration curves of precordial radioactivity are obtained within two minutes of introduction of the tracer into the circulation, this method permits rapid repeated measurements of regional blood flow. Certain considerations must be taken into account, however, when attempting to interpret the results of such flow determinations. Areas of myocardium with impaired circulation may receive only small amounts of the tracer compared to the major volume of tissue perfused and, hence, contribute relatively little to the washout curve. In addition, when one measures the rate of clearance of a radioactive gas, the result reflects both blood flow and volume of distribution of the tracer, clearance rate being related directly to the former but inversely to the latter. If flow and volume change proportionately, there will be no difference in the rate of washout and thus no change in flow will be detected.[12]

In the studies reported here, the coronary catheter was not manipulated between isotope injections and since it seems unlikely that nitroglycerin would produce a decrease in the volume of tissue being perfused, the increase in clearance rate of myocardial radioactivity observed in some of the subjects after drug administration most likely reflects an actual increase in regional blood flow.

The early increase in myocardial blood flow after sublingual nitroglycerin administration was quite transient and presumably accounts for the inability of previous studies to detect this response using the nitrous oxide[4] or rubidium-84 methods since they require a ? to 15 minute period of measurement. Bernstein and associates[9] utilizing the xenon 133 method could not demonstrate increases in myocardial blood flow after sublingual nitroglycerin; however, they did not start their measurements until three minutes after drug administration.

Due to certain limitations, the number of subjects we were able to study was small. Nevertheless, we feel that the results tend to substantiate the biphasic theory of action of nitroglycerin in some patients with arteriographically demonstrable coronary artery disease. Whether or not this biphasic action is responsible for the beneficial effects of the drug during

an anginal attack however remains to be demonstrated.

The actual hemodynamic events which can occur during an anginal attack and the subsequent administration of nitroglycerin are shown in Gorlin's[2] reported observations on myocardial blood flow made during a spontaneous episode of angina in a patient with severe coronary disease. At the time of pain hypertension and a relative tachycardia were noted and myocardial flow was 51 ml per minute per 100 Gm. A control measurement taken earlier during the study when the patient was normotensive was 71 ml per minute per 100 gm. Nitroglycerin was administered sublingually resulting in a rapid increase in myocardial blood flow to 88 ml. per minute per 100 Gm and thereafter relief of pain and return of blood pressure pulse and electrocardiogram to base line.

The changes in myocardial blood flow after nitroglycerin in the subjects with myocardial disease is of some interest. The oxygen requirements of an enlarged hypertrophied ventricle are increased due to an increase in number of contractile elements[13] and the increased wall tension required to maintain a systolic ventricular pressure.[14] At the same time, myocardial capillary concentration falls in proportion to the increase in fiber size and heart weight[15] resulting in a relative decrease in capillary blood supply. Presumably under these circumstances a coronary reserve no longer exists and with increased myocardial oxygen demand angina pectoris and cardiac lactate production can occur in the absence of coronary disease[2] as exemplified by Subject P. B.

The decrease in myocardial blood flow following nitroglycerin administration in these patients is probably related to a decrease in ventricular size produced by the drug[16,17] with a consequent decrease in the ventricular tension time index and a corresponding decrease in myocardial oxygen requirements.[18]

Summary

Using selective intracoronary injections of xenon 133 in saline the effect of sublingual nitroglycerin on myocardial blood flow was studied in nine patients undergoing cardiac catheterization. One normal patient showed a 14 per cent increase in flow 1½ minutes after drug administration with a subsequent decline to 8 per cent below control at 6 minutes. Four of five patients with coronary artery disease showed increased flows of 3 to 13 per cent at 1½ to 2 minutes after taking the drug. In two of these subjects flow decreased to 10 to 23 per cent below control at 5½ minutes. In the remaining three subjects with cardiomegaly and left ventricular hypertrophy nitroglycerin produced a decrease of 7 to 12 per cent in myocardial blood flow at 1½ minutes and a further reduction to 15 to 17 per cent below control in two of the subjects at 5 minutes.

These results are felt to substantiate the theory that in some patients with coronary artery disease nitroglycerin exerts a biphasic action with an initial increase in myocardial blood flow followed by a decrease in flow as the systemic effects of the drug become manifest. This biphasic action was not seen in patients with cardiac enlargement and hypertrophy.

REFERENCES

1. Brunton, T. L. Lectures on the action of medicines, Goodman, L. S. and Gilman, A., editors The pharmacological basis of therapeutics, ed. 2, New York, 1958, The Macmillan Company p. 730.
2. Gorlin, R. Pathophysiology of cardiac pain Circulation 32:138, 1965.
3. Kountz, W. B. Studies on the coronary arteries of the human heart, J. Pharmacol. & Exper. Therap. 45:65, 1932.
4. West, J. W. and Guzman, S. V. Coronary dilatation and constriction visualized by selective arteriography Circulation Res. 7:527, 1959.
5. Likoff, W., Kasparian, H., Lehman, J. S. and Segal, B. L. Evaluation of coronary vasodilators by coronary arteriography Am. J. Cardiol. 13:7, 1964.
6. Gorlin, R., Brachfeld, N., MacLeod, C. and Bopp, P. Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricle work, Circulation 19:705, 1959.
7. Hollander, W., Madoff, I. M. and Chobanian, A. V. Local myocardial blood flow as indicated by the disappearance of NaI 131 from the heart muscle. Studies at rest, during exercise and following nitrite administration J. Pharmacol. & Exper. Therap. 139:53, 1963.
8. Loeb, E. D., Cohen, A., Zaleski, E. J. and Bing, R. J. Effect of nitroglycerin, intensain, isoptin, and papaverine on coronary blood flow in man, Am. J. Cardiol. 17:535, 1966.
9. Bernstein, L., Friesinger, G. C., Lichtlen, P.

R. and Ross, R. S. The effect of nitroglycerin on the systemic and coronary circulation in man and dogs, Circulation 33:107, 1966.
10. Ross, R. S., Ueda, K., Lichtlen, P. R., and Rees, J. R.: Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries, Circulation Res. 15:28, 1964.
11. Herd, J. A., Hollenberg, M., Thorburn, G. D., Kopald, H. H., and Barger, A. C.: Myocardial blood flow determined with krypton-85 in unanesthetized dogs, Am. J. Physiol. 203:122, 1962.
12. Wagner, H. N., Jr.: Regional blood flow measurement with krypton-85 and xenon-133. In Knisely, R. M., and Tauxe, W. N., editors: Dynamic clinical studies with radioisotopes. AEC Symposium series, Oak Ridge, Tenn., 1964, United States Army and Engineering Corps, Division of Technical Information, p. 189.
13. Linzbach, A. J.: Heart failure from point of view of quantitative anatomy, Am. J. Cardiol. 5:370, 1960.
14. Braunwald, E., Ross, J., Jr., and Sonnenblick, E. H.: Mechanisms of contraction of the normal and failing heart, New England J. Med. 277:1012, 1967.
15. Roberts, J. T., and Wearn, J. T.: Quantitative studies on the capillary muscle relationship in human hearts during normal growth and hypertrophy, Am. Heart J. 21:617, 1941.
16. Perloff, J. G., Ronan, J. A., Jr., and deLeon, A. C., Jr.: The effect of nitroglycerin on left ventricular wall tension in fixed orifice aortic stenosis, Circulation 32:204, 1965.
17. Williams, J. F., Jr., Glick, G., and Braunwald, E.: Studies on cardiac dimensions in intact unanesthetized man. V. Effects of nitroglycerin, Circulation 32:767, 1965.
18. Sarnoff, S. J., Braunwald, E., Welch, G. H., Jr., Case, R. B., Stainsby, W. N., and Macruz, R.: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index, Am. J. Physiol. 192:148, 1958.

Cardiac function following prosthetic aortic valve replacement

*Herbert N. Hultgren, M.D.**
*Harold Hubis, M.D.***
*Norman Shumway, M.D.****
Palo Alto, Calif.

Prosthetic and homograft replacement surgery has offered for the first time restoration of essentially normal mechanical valvular function to patients with aortic valve disease, irrespective of the nature of the deformity. Excellent function of prosthetic replacements for as long as 5 years after operation has been observed. Postoperative studies have demonstrated only a small pressure gradient across the prosthesis at rest, with a slightly higher value during exercise.

Several workers have examined cardiac function after aortic valve replacement. Some have studied hemodynamics in the immediate postoperative period[1,2] or examined the effect of a special type of prosthesis. Studies by Judson, Bristow, Ross,[7] Lewis,[8] and Björk[4] and their associates approximately 9 months after surgery have revealed abnormal hemodynamics at rest and during exercise in about 20 per cent of patients. Linhart and Wheat noted abnormal cardiac function in 70 per cent of 20 patients studied 12½ months after surgery but these patients had a high incidence of preexisting coronary disease.

It is the purpose of this study to examine cardiac function after aortic valve replacement (Starr-Edwards prosthesis) in patients who have had a good clinical result from operation.

Methods and materials

Nineteen patients were selected for the study. Preoperative hemodynamic studies had been performed in 17 of these patients. The postoperative studies were performed from 2 to 19 months after surgery (mean interval 8.5 months). No patient had significant disease of the mitral or tricuspid valve. Only 2 patients (Nos. 15 and 16) had clinical evidence of preoperative coronary artery disease. Preoperative coronary arteriograms were not performed. Only 1 patient (No. 18) had evidence of a postoperative prosthetic leak in the form of a Grade 2/6 diastolic blowing murmur at the

From the Division of Cardiology, Department of Medicine, Stanford University School of Medicine, Palo Alto, Calif.
Supported in part by United States Public Health Service grant (HE 5440) and the Santa Clara and San Mateo Heart Associations.

Received for publication July 22, 1968.
*Professor of Medicine, Stanford University School of Medicine, Palo Alto, Calif. Mailing address: Herbert N. Hultgren, M.D., Cardiology Division, Room C-220, Stanford Medical Center, 300 Pasteur Drive, Palo Alto, Calif. 94305.

**Associate Director, Cardiology Department, Santa Clara Valley Medical Center, San Jose, Calif.

***Professor of Surgery, Stanford University School of Medicine, Palo Alto, Calif.

upper left sternal edge. Eight patients had severe aortic stenosis and 4 had persistent left ventricular failure prior to surgery. Eleven patients had severe aortic insufficiency and 5 had left ventricular failure prior to surgery. Left ventricular failure was defined on the basis of clinical symptoms, clinical signs, and a mean resting pulmonary artery wedge pressure exceeding 12 mm. Hg above the mid-chest.

Clear clinical improvement was noted for all patients since they were selected for the study largely on this basis. The degree of improvement was substantial. Prior to surgery, 3 patients were in Class II (New York Heart Association Criteria), 14 patients were in Class III, and 2 patients were in Class IV. At the time of the postoperative study, 17 patients were in Class I and 2 patients were in Class II. Normal physical activity was carried out without symptoms by all patients. All previously employed patients had returned to work. Thirteen patients were no longer taking medication (except anticoagulants) or observing any dietary restriction of sodium. Pertinent clinical data are summarized in Table I.

Valve replacement (Starr-Edwards prosthesis) was performed in a manner which has been previously described.[14] Hemodynamic studies were performed using the same technique that has been employed to study the hemodynamic effect of mitral valve replacement surgery.[12] Data were compared with normal values employed in the previous study.[12] Pre- and postoperative roentgenograms of the chest were compared and the cardiothoracic ratio was determined. Preoperative 12 lead electrocardiograms were compared with postoperative tracings.

Results

The results of the hemodynamic studies are summarized in Tables II and III. The cardiac index at rest exceeded 2.4 L. per minute per square meter in all but [illegible] patients.

Table I. Clinical data before and after aortic valve replacement surgery

Patient	Sex	Age	Lesion	LV failure	Rhythm	Decrease heart size (x-ray) (0-3)	Decrease in LVH (ECG) (0-3)	Post-op infarct	Func. Class (pre-op)	Func. Class (post-op)	Follow-up time (months)
1. B. P.	F	30	AI	0	S	3	0	0	2	1	7
2. A. D.	M	46	AI	0	S	0	1	+	3	1	12
3. R. H.	M	31	AI	0	S	2	0	0	2	1	6
4. H. K.	M	39	AI	0	S	1	0	+	4	1	6
5. J. T.	M	57	AI	+	S	2	0	+	3	1	19
6. W. M.	M	56	AI	+	S	3	0	+	3	1	6
7. F. B.	M	23	AI	+	S	2	0	0	2	1	3
8. C. N.	M	30	AI	0	S	2	0	0	3	1	2
9. R. C.	M	50	AS	0	S	2	3	0	3	1	9
10. E. J.	F	47	AS	0	S	1	3	0	3	1	6
11. K. W.	M	41	AS	0	S	1	3	0	3	2	12
12. L. O.	M	46	AS	+	S	3	3	+	3	1	10
13. J. M.	M	64	AS	+	S	2	3	+	3	1	11
14. C. C.	M	48	AS	+	S	3	2	0	3	1	7
15. I. G.	M	39	AS	+	S	2	0	+	3	1	9
16. L. H.	M	66	AS	+	S	3	3	RBBB	3	1	12
17. H. W.	M	42	AI	+	S	3	2	0	3	1	11
18. F. J.	F	44	AI	0	S	3	2	0	3	2	5
19. H. W.	M	56	AI	+	AF	3	2	0	4	1	8

Abbreviations: LV, left ventricular; LVH, left ventricular hypertrophy; AI, aortic insufficiency; AS, aortic stenosis; RBBB, right bundle branch block; S, sinus rhythm; AF, atrial fibrillation.

Decrease in heart size by roentgenogram and decrease in left ventricular hypertrophy in the electrocardiogram are graded from 0 to 3. 0 indicates no essential change; 3 indicates return to a normal heart size or a normal ECG. Functional classification according to the New York Heart Association.

The resting A V difference was less than 5.0 ml. per 100 ml. in all but 3 patients. During exercise the exercise factor exceeded 500 in all but 3 patients and the A V difference was less than 10 0 ml per 100 ml in all but 3 patients.

Pressure studies also revealed essentially normal values. The pulmonary artery mean pressure at rest was less than 18 mm in all but 3 patients, and the pulmonary artery wedge pressure at rest was less than 12 mm in all but 1 patient During exercise the pulmonary artery mean pressure exceeded 40 mm. Hg in only 3 patients, and the pulmonary artery wedge pressure exceeded 14 mm. in only 2 patients.

Roentgenographic decrease in heart size was observed in 18 patients and the magnitude of the decrease is summarized in Table I Eight patients had a normal heart size after surgery compared to only 1 patient prior to operation. Patients with preoperative heart failure had the greatest decrease in heart size.

Prior to operation 18 patients had electrocardiographic evidence of left ventricular hypertrophy After operation there was a variable degree of regression toward a normal record Persistence of a left ventricular hypertrophy pattern was observed in 8 patients (44 per cent) A striking regression occurred in 6 patients (33 per cent) so that the final follow-up record was within normal limits. In 3 patients, p waves demonstrated less deep inversions in Lead V after surgery The changes in the electrocardiogram (ECG) could not be related to changes in heart size in the roentgenogram or to persisting hemodynamic abnormalities. For example Fig 1 illustrates the persistence of a left ventricular hypertrophy pattern in the ECG of a patient (No 1) who had a marked decrease in heart size following surgery and who had normal postoperative hemodynamics. This patient's chest roentgenogram is illustrated in Fig 2 Fig 3 demonstrates complete return to the ECG to normal in a patient

Table II Aortic replacements—*Preoperative hemodynamic data*

Patient	PA mean (mm. Hg)		PA wedge (mm. Hg)		Cardiac index (L /min / M)		A V dif (ml /100 ml)		O consump (ml /M)		PAR units	BSA (M)	Exercise factor
	R	E	R	E	R	E	R	E	R	E			
1, B. P	20		12		2 9		4 2		125		1 8	1 64	
2, A. D	14	25	8	12	1 8	3 6	6 1	9 2	112	335	1 8	1 80	810
3, R H.	20	28	12	16	3 2	4 8	5 3	10 0	167	485	1 6	1 60	635
4 H. K.	—	—	—	—	—	—	—	—	—	—	—	—	—
5, J T	51		36		1 7		9 2		164		5 9	1 54	
6 W M	42		27		3 0		3 8		175		3 0	1 62	
7 F B.	17	49	8	34	3 6	5 6	5 2	10 9	186	624	1 7	1 56	457
8, C. N	15		12		2 6		6 5		171		6	1 84	
9 R. C.	13		6		2 2		6 1		134		1 8	1 81	
10, E. J	13		7		1 8		7 22		130		2 0	1 67	
11, K. W	11		8		3 5		4 28		147		4	2 0	
12, L. O.	17		14		4 3		4 10		176		4	2 0	
13 J M.	22		16		2 9		5 10		145		1 2	1 7	
14 C. C.	31	59	21	31	2 4	3 8	6 51	11 32	158	439	2 3	1 8	494
15, I G.			12		5 2		3 20		169				
16, L. H.			70		2 9		5 08		244			1 6	
17 H. W	—	—	—	—	—	—	—	—	—	—	—	—	—
18, F J	22		13		4 1		3 40		138		1 4	1 51	
19 H. W	30		17		1 7		10 4		170		4 2	1 8	
Mean	22 6	40 3	14 6	23 2	2 9	4 45	5 7	5 65	159	470	1 8	1 62	600
Range	11 52	25– 59	6–36	12– 34	1 7 5 2	3 6– 5 6	3 2 10 4	9 2– 11 32	112 244	355– 624	4– 4 2	1 51– 2 0	457–810

Abbreviations. PA, Pulmonary arterial; PAR, pulmonary arterial resistance; R, rest; E, exercise.
*Patient No. 7 H. W had small ventricular septal defect which was closed at the time of his aortic valve replacement.

(No 11) with only a moderate postoperative decrease in heart size. Patients with preoperative aortic insufficiency showed little regression of the ECG toward normal.

In 6 patients, electrocardiographic signs of transmural myocardial infarction appeared early in the postoperative period usually within 72 hours after surgery Two examples are illustrated in Figs. 4 and 5 Aside from the occurrence of cardiac arrhythmias, the usual signs of infarction such as chest pain friction rub gallop rhythm and hypotension were not evident or were obscured by abnormalities of the immediate postoperative period

Serial changes in serum glutamic oxalacetic transaminase (SGOT) and serum lactic dehydrogenase (LDH) were studied in 4 patients (Nos. 2 6 12 and 13) with postoperative infarct patterns. The values were compared with those observed in 27 patients not demonstrating signs of infarction (Fig 6) A high SGOT value of 148 units 72 hours after surgery was observed in 1 patient with infarction. Enzyme values of SGOT in the other infarct patients were slightly higher than in patients without infarction but these values were similar to those found by Baer and Blount[12] following open heart operations not involving valve replacement Levels of LDH were no different in the infarct group compared to control patients, but this enzyme is also affected by hemolysis which is frequently present after valve replacement surgery The postoperative convalescence of the infarct patients was not unduly prolonged and none of the patients experienced effort angina after return to normal activity Three had residual hemodynamic abnormalities which could be related to infarction

Discussion

Essentially normal cardiac function both at rest and during moderate exercise was observed in 14 of 19 patients in this study (74 per cent) All the patients had been

Table III Aortic replacements—Postoperative hemodynamic data

Patient	PA mean (mm Hg)		PA wedge (mm Hg)		Cardiac index (L./min./M²)		A V diff (ml./100 ml.)		O₂ consump (ml./M²)		PAR units	BSA (M²)	Exercise factor
	R	E	R	E	R	E	R	E	R	E			
1 B P	12	24	7	16	4 0	5 2	3 7	7 6	146	400	76	1 65	470
2, A. D	17	24	10	11	2 5	4 0	3 9	8 3	92	328	1 6	1 80	630
3 R H	13	19	4	6	4 2	6 5	3 4	9 1	160	520	1 3	1 62	890
4 H K.	14	48	6	12	2 2	4 1	5 8	10 0	125	371	2 1	1 74	770
5 J T	15	52	9		2 4	3 5	6 3	12 8	153	445	1 5	1 71	330
6, W M	12	30	5	9	3 0	4 9	4 5	8 8	165		1 4	1 66	
7 F B.	13	22	8	10	3 9	5 8	4 7	8 6	161	488	9	1 56	860
8 C. N	11	12	8	9	3 2	4 1	4 7	10 7	148	436	5	1 85	210
9 R C.	13	23	8	10	3 0	4 5	5 1	9 3	154	420	9	1 86	570
10, E. J	18	27	3	8	2 8	4 2	4 6	8 2	128	336	3 1	1 68	670
11 K. W	11	13	10	7	3 3	3 0	3 9	8 2	128	402	2	2 0	625
12. L. O.	13	21	8	13	3 3	4 5	4 6	9 6	150	431	8	2 0	425
13 J M	12	24	5	10	3 2	5 3	4 5	9 7	146	510	1 3	1 7	375
14 C. C.	21	30	9	12	3 8	6 9	4 0	6 9	152	474	1 7	1 9	960
15 I G	25	41	15	20	3 9	5 3	4 0	7 5	153	400	1 3	2 0	560
16 L. H					4 6		3 4		151			1 6	
17 H. W	12	18	5	8	3 9	5 3	3 9	7 8	150	412	5	2 2	510
18, F J	14	23	8	13	3 4	6 6	3 8	6 0	128	395	1 3	1 4	1700
19 H W	12	20	7	9	3 4	4 9	4 8	7 8	163	381	1 5	1 8	680
Mean	14 5	26 6	7 4	10 9	3 36	5 04	4 64	8 8	144	424	1 3	1 4	1200
Range	11 25	12 48	4 15	6-20	2 2- 4 6	4 0- 6 9	3 4- 6 3	6 0- 10 7	92 165	329- 520	2- 2 1	1 4- 2 0	210- 1700

See legend Table II for abbreviations.

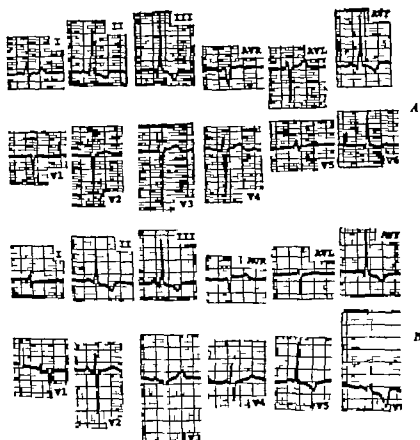


Fig. 1. ECG' of Patient No. 1 B. P. *A*, Before aortic valve replacement. *B*, 14 months after aortic valve replacement for aortic insufficiency. Persistence of left ventricular hypertrophy pattern despite decrease in heart size in chest roentgenogram.



Fig. 2. Chest roentgenogram of Patient No. 1 B. P. with aortic insufficiency showing decrease in cardiac size 12 months after aortic valve replacement.

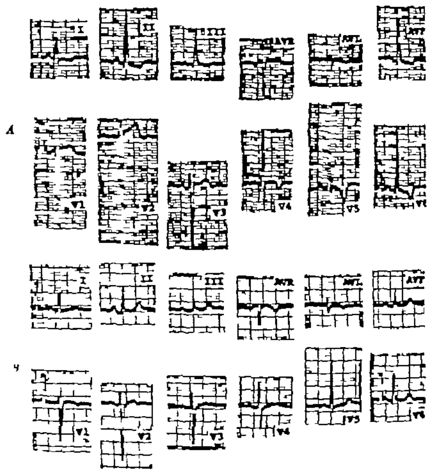


Fig 3 ECG of Patient No 11 K. W A Before aortic valve replacement. B 1 year after aortic valve replacement for aortic stenosis Note reversal of left ventricular hypertrophy pattern

selected because they had demonstrated excellent clinical results from aortic valve replacement surgery

Three patients who exhibited moderate residual hemodynamic abnormalities are described in the following Patient No 4 had a cardiac index of 2 2 L. per minute per square meter at rest with an A V difference of 5 8 ml per 100 ml. Pulmonary artery pressure was normal at rest, but rose to 48 mm (mean) during exercise with a 6 mm rise in wedge pressure. This patient exhibited electrocardiographic evidence of myocardial infarction within the first 72 hours after surgery and abnormal Q waves were still present in the ECG 2 years later Patient No 5 had a cardiac index of 2 4 L. per minute per square meter and an A V difference of 6.3 ml per 100 ml. at rest The exercise factor was 330 Pulmonary artery pressure was normal at rest but rose to 37 mm (mean) during exercise. The preoperative ECG was suggestive of old myocardial infarction so that underlying coronary disease could have been present. Coronary arteriography was not performed Two years after the operation clinical signs of progressive mitral insufficiency appeared and this required mitral valve replacement in March 1968 At surgery several ruptured chordae were noted Patient No. 15 had a normal cardiac output and A V difference The exercise factor was 560 At rest the pulmonary artery pressure was 25 mm (mean) and the wedge pressure was 15 mm, rising to 41 mm and 20 mm respectively during exercise. This patient had a debridement operation for aortic stenosis in November 1961 Following this operation a QS complex appeared in Leads III and aVF consonant with inferior

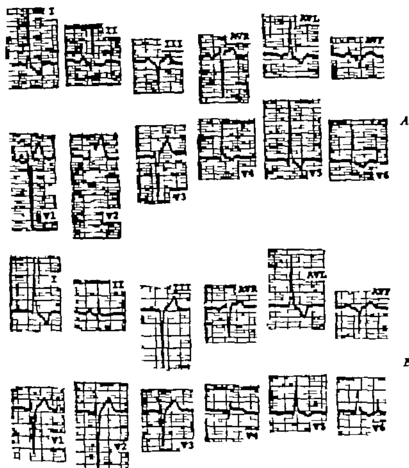


Fig. 4 ECG of Patient No. 15 I G 4 Before aortic valve replacement. B 5 months after aortic valve replacement. Note QS deflection in Leads III and V compatible with old inferior wall infarction in initial record. Following surgery an abnormal QRS complex and persistent S-T elevation has appeared in V compatible with anterior wall infarction.

myocardial infarction (Fig. 4). He experienced moderate clinical and hemodynamic improvement, but subsequently became more symptomatic and had aortic valve replacement in July 1965. Following this operation a Q wave appeared in V consonant with anterior wall infarction. An analysis of all abnormalities in cardiac function, using as normal values those given in Table VI reveals an incidence of 12.5 per cent abnormal values out of a total of 162 possibilities. The 3 patients described above accounted for 64 per cent of the total abnormalities.

Hence 3 patients with moderate residual hemodynamic abnormalities had evidence in the ECG of either acute myocardial infarction following surgery (No 4) probable infarction prior to operation (No. 5) or infarction both prior to and after surgery (No 15). All 3 had residual abnormalities in the ECG consonant with old infarction 2 years after surgery.

Causes of residual cardiac dysfunction after valve replacement surgery have recently been examined by Peterson. Prosthesis insufficiency, prosthesis obstruction, uncorrected valve disease, and myocardial disease were the most frequent factors involved. Linhart and Wheat have emphasized the importance of preexisting coronary artery disease in cardiac dysfunction following aortic valve replacement.

The response to isoproterenol infusion was normal and the increase in heart rate and cardiac output was similar to that observed in patients following mitral valve replacement surgery.[11] During the infusion

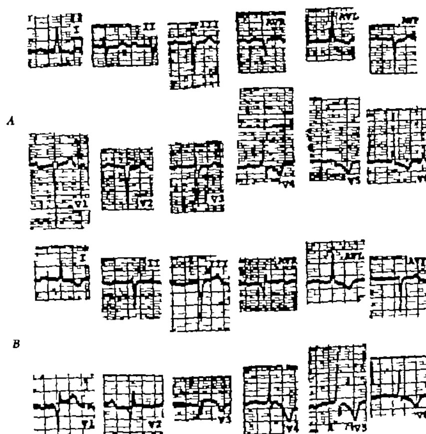


Fig. 5. ECG of Patient No. 6, W. M. *A*, Before aortic valve replacement. *B*, 11 days after aortic valve replacement. Note appearance of abnormal Q waves in Leads V and decrease in QRS voltage of Lead V compatible with anterior wall infarction.

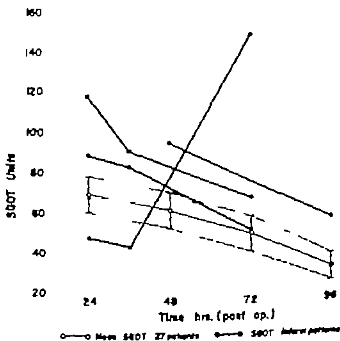


Fig. 6. SGOT values in 5 patients who had postoperative electrocardiographic evidence of myocardial infarction compared to values observed in 20 patients with aortic or mitral valve replacement surgery who demonstrated no evidence of myocardial infarction. Enclosed area is equal to two standard deviations.

the wedge pressure decreased from 8.6 mm to 6.0 mm, while in patients following mitral valve replacement the wedge pressure did not change significantly (8.2 mm to 8.0 mm.) probably because of the obstruction to flow due to the mitral prosthesis (Fig. 7 and Table IV).

Pulmonary arteriolar resistance decreased following operation. Similar observations have been made following mitral valve replacement where a greater degree of pulmonary hypertension is present.[11,14]

The excellent degree of hemodynamic improvement observed in the present study is in accord with the observations of other workers whose data are summarized in Table V. All of the patients probably did not manifest good clinical results, hence residual cardiac dysfunction was more frequently observed.

The capacity to obtain a good clinical and hemodynamic result from aortic valve replacement surgery was not affected by either the nature of the preoperative lesion or the presence of congestive failure prior to operation.

Left heart pressures were not measured in the present study. Such data provide additional information regarding left ventricular function. Ross and associates[7] made left ventricular pressure measure-

Table IV. Effect of infusion of isoproterenol in patients who have had aortic valve replacement

Parameter	Control		Isuprel	
	Mean	*Range*	*Mean*	*Range*
PA pressure (mean) (mm. Hg)	16.2	11–43	16.1	11–48
PA wedge pressure (mean) (mm. Hg)	8.6	4–24	6.0	3–20
Cardiac index (L./min./M.²)	3.30	2.3–4.2	4.55	3.3–6.3
Arteriovenous O_2 diff. (ml./100 ml.)	4.6	3.4–7.2	3.7	2.9–5.6
Oxygen consump. (ml./min./M.²)	182	128–286	205	144–305
Heart rate/min.	72.5	60–89	96.5	90–126

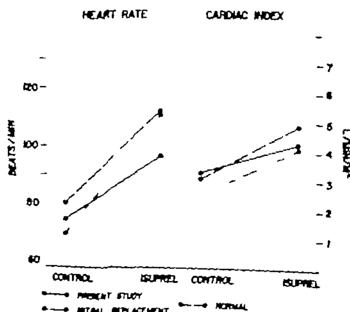


Fig. 7. Comparison of hemodynamic response to isoproterenol following aortic and mitral valve replacement.

Table V Hemodynamic values for patients who had prosthetic aortic valve replacement

Group	PA pressure (mean) (mm. Hg)		PA wedge or left atrial pressure (mm. Hg)		Cardiac index (L./min./M.²)		A-V diff. (ml./100 ml.)		Exercise factor	Aortic gradient (mm. Hg mean)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise		Rest	Exercise
Present study	16	29.5	8.4	13.8	3.3	4.9	4.5	8.5	645		
Judson*	17	31	9	21	3.0	5.0	4.9	8.9	760	18.0	
Ross					3.0	4.3			730	12.4	11.4
Bristow			6.4	8.2	2.6	3.7	5.4	8.3	440	20.8	21.5
Beck	14.6	49	5		3.0	5.2				28.0	47.8
Linhart			17†	15‡	2.8	4.4	5.8	9.7	600	14.4	
Bjork*					3.3	7.0				11.3	37.0
M	15.8	36.3	9.2	14.5	3.0	4.9	5.1	8.8	635	17.5	30.0

*University of Cape Town prosthesis.
†Left ventricular diastolic pressure, 20 patients.
‡Left ventricular diastolic pressure, 7 patients.

tients at rest and during exercise in evaluating the results of aortic valve replacement surgery in 14 patients. In 9 patients hemodynamic abnormalities were present which would have been detected by right heart catheterization techniques. In 3 patients left ventricular diastolic pressure during exercise rose more than 5 mm. but the final measurement did not exceed 12 mm. These abnormalities may not be detected by right heart catheterization techniques. One patient in the present study (No. 4) had an increase in wedge pressure of more than 5 mm. with a final measurement of less than 14 mm. Other abnormalities were present, however. Thus, the advantage of direct left heart pressure studies over right heart techniques is small at present. Further refinements of methodology, such as the inclusion of left ventricular volume studies, will clearly make such techniques much more sensitive in evaluating left ventricular function in the future.

Left ventricular function following aortic valve replacement has been investigated by two workers who used angiotensin as a method of increasing left ventricular pressure work. Kelly[14] found that 8 of 20 patients had normal function, 6 had borderline function, and 6 had abnormal left ventricular function. All but 2 patients had a normal resting cardiac index and a normal left ventricular diastolic pressure, but details are not presented and exercise was not performed. Linhart and Wheat found that responses to angiotensin were abnormal in 7 of 9 patients studied in a similar manner. Angiotensin may not be a suitable drug for such studies since it may constrict coronary vessels and impair ventricular performance by reducing coronary blood flow.[17]

It is clearly apparent from studies of cardiac function following aortic valve replacement that cardiac output is higher at rest and during exercise than following mitral valve replacement (Table VI). These differences are also apparent in the immediate postoperative period.[1] Cardiac output has also been shown to be higher in aortic stenosis compared to mitral stenosis both at rest and during exercise prior to surgery.[1,22] The mechanism of the low cardiac output seen in mitral stenosis before and after valve replacement surgery has been previously reviewed.[1] Two factors appear to be involved: (1) a myocardial factor which may be related preoperatively to scarring and fibrosis of the mitral valve, chordae and papillary muscles and postoperatively related to loss of papillary muscle function; (2) an abnormality in the control of cardiac output either by periph-

Table VI. Comparison of mean values obtained in patients with mitral valve replacement[11] and patients with aortic valve replacement (present study)

Type of replacement	P A pressure		P A wedge pressure		Cardiac index		A V d f		Exercise factor
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	
Mitral	21 5	38 7	8 5	19 4	2 6	3 8	5 4	10 1	510
Aortic	16 4	30 0	8 7	14 2	3 3	4 8	4 6	9 4	680
Normal range	10–18	14–30	4–10	8–14	2 5–5	4 0–7 5	3–5	6–10 0	>500

eral or central mechanisms which is not reversed by correction of the valvular deformity The latter mechanism has been suggested as the cause of residual cardiac dysfunction following relief of valvular pulmonic stenosis.[32] Further studies of such mechanisms are clearly needed

Useful indirect information regarding cardiac function after aortic valve replacement is provided by changes in cardiac size determined by the roentgenogram regression of hypertrophy patterns in the ECG and the appearance of electrocardiographic evidence of myocardial infarction following surgery

In the present study a decrease in heart size was observed in all but 1 patient (No. 2) who had a normal heart size before surgery Rastelli and associates[34] noted a decrease in heart size in 79 per cent of 18 patients studied 10 7 months (mean) after aortic valve replacement. Björk and Cullhed[3] noted a decrease in calculated heart volume in 80 per cent of 20 patients. Gotsman and associates[35] noted a return to a normal heart size in 15 per cent of 25 patients with aortic valve replacement who were studied one year after operation These workers included patients in their study who had less than an excellent clinical result from surgery In addition the changes in heart size by x-ray suggest that in some patients the ECG remains abnormal despite a decrease in left ventricular size and presumably left ventricular mass. Similar observations have been made by Lewis and associates.[36] The reason for the more frequent persistence of left ventricular hypertrophy patterns in patients with aortic insufficiency compared to patients with aortic stenosis remains unexplained It is possible that ventricular hypertrophy with dilatation (diastolic overload) is less likely to regress than concentric ventricular hypertrophy (systolic overload)

In our experience electrocardiographic changes consonant with acute myocardial infarction are a significant complication of aortic and mitral valve replacement surgery It has been observed in our hospital in 15 additional patients not included in this report. These observations were made over a two year period when approximately 170 aortic valve replacement operations were performed Autopsy studies performed in 6 of these patients confirmed the clinical diagnosis of acute infarction. In 5 patients, the coronary arteries were normal and no occluding thrombus or embolus could be found One of these patients is described in a previous report [37] Dreifus and associates[38] have made similar observations. They reported on 72 patients with Starr Edwards prostheses. Acute infarction patterns were observed after operation in the ECG's of 18 patients. Transient bundle branch block was observed in 9 and permanent bundle branch block was seen in 13 In 19 operative deaths, 13 necropsies were performed and either acute myocardial infarction or myocardial necrosis was observed in 6. The coronary arteries were free of obstructive lesions in all but one heart. Roberts and Morrow[39] listed acute myocardial infarction as the third most frequent fatal complication following insertion of the Starr Edwards prosthesis. This was observed in 16 of 350 patients (4.6 per cent) However all infarcts were noted after mitral valve replacement and none were described after aortic valve re-

placement Gooch[38] noted 3 postoperative infarctions after 132 open heart operations which were largely valve replacements. Two patients age 6 and 32 years, had typical electrocardiographic changes appearing in the intensive care unit. Both recovered A 50-year-old man with aortic and mitral valve replacement died suddenly on the thirteenth postoperative day Autopsy revealed extensive subendocardial infarction Coronary artery disease was present and a recent thrombotic occlusion was present in the left anterior descending branch [1]

The cause of myocardial infarction following valve replacement surgery is not evident. In most patients preexisting coronary disease was not present and normal coronary arteries were noted at autopsy Ischemic injury to the myocardium may occur particularly in the presence of left ventricular hypertrophy due to inadequate coronary perfusion long bypass times, and low postoperative blood pressure.

Morales and his workers[39] reported on autopsy findings on 13 patients who had a low cardiac output following valve replacement surgery The principal findings varied from disruption of individual fibers to massive necrosis The lesions were multiple and not distributed along the course of coronary vessels. They were often localized to the apex which was shown by postmortem arteriography to be poorly vascularized No clear etiology was implicated

In dogs experimental air embolism involving the coronary arteries has been shown to result in myocardial infarction and consequent changes in the ECG[40] However this seems an unlikely cause of postoperative myocardial infarction since it is usually evident at the time of surgery No difficulty was encountered at the time of operation in restoring cardiac rhythm in the patients described in this report. The possibility of delayed air embolism remains, however Embolism of the coronary arteries by thrombi originating on the prosthesis is another possibility[36] Lysis of the thrombus after the occurrence of infarction may account for the failure to find an occluding embolus at autopsy

It is evident from data in the present paper that postoperative myocardial infarction which may be evidenced only by changes in the ECG may result in late residual cardiac dysfunction.

Summary

1 Hemodynamic and clinical studies have been performed in 19 patients judged as having had excellent clinical results from aortic prosthetic valve replacement surgery

2 Following aortic valve replacement, essentially normal cardiac function was present in 74 per cent of the 19 patients. Cardiac function was more normal after aortic valve replacement than after mitral valve replacement.

3 Three patients who had persisting moderate impairment of cardiac function had experienced myocardial infarction either before operation or immediately after surgery

4 Electrocardiographic evidence of myocardial infarction appeared in the immediate postoperative period in 6 of the 19 patients. The data indicate that infarction resulted from surgery in the absence of pre-existing coronary disease in 5 patients.

5 Reversal of electrocardiographic signs of left ventricular hypertrophy occurred in 42 per cent of patients. Regression of hypertrophy patterns was most commonly observed in patients with pure aortic stenosis while little change occurred in the ECGs of patients with pure aortic insufficiency Persistence of hypertrophy patterns was not associated with impaired cardiac function

6 Decrease in heart size in the roentgenogram occurred in 18 of 19 patients. The greatest decrease in size occurred in those with heart failure prior to surgery

REFERENCES

1 Starr A., Edwards, L., McCord, C., and Griswold, H Aortic replacement. Clinical experience with a semi-rigid ball-valve prosthesis Circulation 27 779 1963.

2. Rastelli, G and Kirklin J Hemodynamic state early after replacement of aortic valve with ball-valve prosthesis, Surgery 61 873, 1967

3 Austen W Corning H Moran, J Sanders, C., and Scannell, J Cardiac hemodynamics immediately following aortic valve surgery J Thoracic & Cardiovas. Surg 51 461 1966.

4 Beck W Barnard, C., and Schrire V The hemodynamics of the University of Cape Town

aortic prosthetic valve Circulation 33:517 1966.

5 Judson, W Ardaiz, J Strach, T and Jennings, R., Post-operative evaluation of prosthetic replacement of aortic and mitral valves Circulation 29 (Suppl No. 2) 14, 1964.

6 Bristow D McCord, C., Starr A. Ritzman L., and Griswold H: Clinical and hemodynamic results of aortic valvular replacement with ball-valve prosthesis, Circulation 29 (Suppl. No. 1) 36 1964.

7 Ross, J J Morrow A Mason, D and Braunwald, E. Left ventricular function following replacement of the aortic valve Circulation 33:507 1966.

8 Björk, V and Cullhed, I Functional results with an aortic ball-valve prosthesis, Thorax 22:21 1967

9 Linhart, J and Wheat, M J Myocardial dysfunction following aortic valve replacement J Thoracic & Cardiovas. Surg 54:259 1967

10. Iben, A Hurley E and Shumway N Surgery for combined lesions of the aortic and mitral valves, Am. J Surg 110:262 1965

11 Hultgren, H., Hubis, H. and Shumway N Cardiac function following mitral valve replacement, Am. Heart J 75:302, 1968

12 Baer H and Blount, S. The response of the serum glutamic oxalacetic transaminase to open-heart operation, Am Heart J 60:867 1960.

13. Peterson, C., Herr R., Crisera, R Starr A Bristow J and Griswold, H. The failure of hemodynamic improvement after valve replacement surgery Ann Int. Med. 66:1 1967

14. Krasnow N Rolett, E., Yurchak, P Hood, W and Gorlin R Isoproterenol and cardiovascular performance, Am. J Med. 37:514 1964.

15. Braunwald, E Braunwald, N Ross, J and Morrow A. Effects of mitral valve replacement on the pulmonary vascular dynamics of patients with pulmonary hypertension New England J Med. 273:509 1965.

16. Kelly D Myocardial function (studied using Angiotensin) after aortic homograft valve replacement, New Zealand M J (Supp. No. 64) 1968.

17 Fowler N and Holmes, J Coronary and myocardial actions of angiotensin, Circulation Res. 14 191, 1964.

18. Hancock, E., and Fleming, P Aortic stenosis, Quart J Med. 29:209 1960.

19. Kimball, R., and Hancock, E. Left ventricular function in exercise in aortic stenosis, Clin. Res 15 119 1967

20. Braunwald E. Goldblatt, A. Aygen M Rockoff S., and Morrow A. Congenital aortic stenosis. I Clinical and hemodynamic findings 100 patients, Circulation 27:426, 1963

21 Eliasch H. Pulmonary circulation at rest and on effort in mitral stenosis, Scandinav J Clin. & Lab. Invest. 4 (Suppl. No. 4) 1 1952.

22. Donald, K Bishop J and Wade, O Studies of minute to minute changes of arteriovenous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of steady state during exercise in rheumatic heart disease, J Clin. Invest. 33 1146 1954.

23. Jonsson, B and Lee S Hemodynamic effects of exercise in isolated pulmonary stenosis before and after surgery *Brit. Heart J 30:60 1968*

24 Rastelli, G. Kincaid, O and Kirklin, J Heart size after valve replacement, M y Clinic Proc 41:217 1966

25 Gotsman, M Beck, W Barnard, C and Schrire, V Changes in chest radiograph after aortic valve replacement, Brit Heart J 30:219 1968.

26. Lewis, R Herr R., Starr A and Griswold H Aortic valve replacement with the Starr-Edwards ball-valve prosthesis Indications and results, Am Heart J 71:549 1966.

27 Hurley E. Angell, W Dong, E. Reeves, M and Shumway N Multiple valve replacement, Arch. Surg 91 163 1967

28 Dreifus, L Cannarozzi, N and Rabbino, M Electrocardiographic alterations following prosthetic valve replacement, Circulation (Suppl. III) 70, 1964.

29 Roberts, W and Morrow A Topics in clinical medicine Anatomic studies of hearts containing caged-ball prosthetic valves, B ll. Johns Hopkins Hosp 121:271 1967

30. Gooch, A et al Medical complications following open-heart surgery Arch. I t Med 120:667 1967

31. Gooch, A. S Personal communication.

32 Morales, A., Fine, G., and Taber R. Cardiac surgery and myocardial necrosis, Arch. Path. 83 71 1967

33. Goldfarb, D and Bahnson, H. Early and late effects on heart of small amounts of air in the coronary circulation, J Thoracic & Cardiovas. Surg 46:368, 1963

34. London, B. Myocardial infarction presumably embolic, J A. M A. 201:150, 1967

Control of persistent ventricular ectopic beats by alprenolol, a new beta-adrenergic blocking agent

*Joseph R. Anthony, M.D.**
*Herskel Jick, M.D.***
David H. Spodick, M.D.
Boston, Mass.

The use of an effective beta adrenergic blocking agent, dichloroisoproterenol, in 1958 by Powell and Slater provided a new approach to the treatment of various dysrhythmias. However, it was found that dichloroisoproterenol had a stimulatory effect upon the heart which made its use impractical. Thus in 1962 an improved β-blocking agent, pronethalol, was introduced. Pronethalol was found to have a pure β-adrenergic blocking effect upon the heart, but in repeated use in mice was found to be carcinogenic. In 1964 propranolol was introduced and found also to be a pure β blocking agent without the carcinogenicity of pronethalol. Subsequently much investigation and many articles have appeared on propranolol.

The purpose of this paper is to report our observations on the effects of a new β adrenergic blocking agent, alprenolol (Aptine or H 56/28), in the treatment of ventricular ectopic beats. Alprenolol was introduced in 1966 by A. B. Hassle Laboratory of Sweden[4] and has had limited clinical trial. It differs from propranolol in that it is a derivative of benzene and not naphthalene and has the structure 1 (o-allylphenoxy)-3-isopropylamino-2 propanol hydrochloride (Fig. 1). Its potency is about half that of propranolol when given orally but equal to it when given intravenously.

In preliminary studies in animals in the resting state alprenolol did not significantly decrease the blood pressure, stroke volume, or cardiac output when given intravenously, whereas propranolol consistently reduced these parameters.[3] In human studies, propranolol given intravenously (10 mg.) substantially reduced cardiac output (average 22 per cent) whereas alprenolol in the same dose did not. Both

From the Cardiology and Clinical Pharmacology Departments of the Medical Services, Lemuel Shattuck Hospital and the Department of Medicine, Tufts University School of Medicine, Boston, Mass.
This study was done during the tenure of a Research Fellowship in the Clinical Pharmacology and Cardiology Divisions, Lemuel Shattuck Hospital, and supported in part by Clinical Pharmacology Training Grant No. [illegible]
Received for publication Aug. 1, 1968.
*Junior Consultant in Medicine, Lemuel Shattuck Hospital; Clinical Instructor in Medicine, Tufts University School of Medicine. Reprint requests should be addressed to: Dr. Joseph R. Anthony, Department of Cardiology, Lemuel Shattuck Hospital, 170 Morton St., Boston, Mass. 02130.
**Assistant Professor of Medicine, Tufts University School of Medicine; Director, Division of Clinical Pharmacology, Lemuel Shattuck Hospital.
***Chief, Cardiology Division, Lemuel Shattuck Hospital; Assistant Professor of Medicine, Tufts University School of Medicine; Lecturer in Medicine, Boston University School of Medicine.

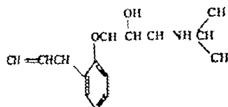


Fig. 1 Structure of alprenolol 1-(o-allylphenoxy)-3-isopropylamino-2-propanol-hydrochloride Aptine H 56/28.

β-blocking agents were equally effective in inhibiting the cardiovascular response to isoproterenol

Since a lowering of blood pressure stroke volume and cardiac output imply a decrease in inotropic performance alprenolol may have a distinct advantage over propranolol in managing rhythm disturbances in patients whose heart muscle is already impaired by disease.

The following is a double-blind crossover study comparing the effect on ventricular ectopic beats of oral alprenolol against a placebo

Materials and methods

Thirteen patients with ventricular ectopic beats persisting for longer than 24 hours were selected from the wards of the Lemuel Shattuck Hospital in Boston and assigned randomly to either the drug alprenolol or a placebo All other forms of therapy were unchanged Patients with clinical evidence of congestive heart failure acute myocardial infarction and asthma were omitted from the study because of possible deleterious effects of the drug Patients with suspected digitalis toxicity were rejected because the more acceptable form of therapy included omitting the digitalis

Twenty milligrams of alprenolol or placebo identically packaged were administered orally every 6 hours starting at 9 A.M on day 1 and continued for a total of five doses terminating at 9 A.M on day 2. The patient remained off the drug or placebo until 9 A.M on day 3 allowing for clearance, and at this time the tablets were switched those getting the drug would now get the placebo and vice versa on the same schedule until the last dose at 9 A.M on day 4 The contents of the medication were unknown to the doctor the nurse administering the drug and the patient.

An electrocardiogram with two one minute rhythm strips of Lead II was taken at 10 A.M on the day prior to beginning the study after a period of 15 minutes with the patient supine, 1 hour before beginning the study on day 1 and day 3 and 1 hour after the second and fifth doses. Thus the records of ventricular ectopic beats were an average of a total of six one minute rhythm strips for the control period and four one-minute rhythm strips for each of the drug and placebo periods. Blood pressure was recorded in the right arm at the time of each electrocardiogram twice by a medical student and twice by the cardiology fellow and then averaged A minimum of eight blood pressure recordings were taken and then averaged for each period The pulse was recorded and averaged from the electrocardiograms.

Also monitored were hematocrit white blood cell and differential count urinalysis, serum creatinine total bilirubin and serum glutamic pyruvic transaminase just prior to beginning the study 1 hour before the last dose on day 2 and the day after the study was completed day 5

Results

Of the thirteen patients selected three were receiving digoxin at the time of the study It is believed that clinically the ectopic beats were not related to the use of digoxin because a trial discontinuation of the drug for five days failed to stop the extrasystoles There was a significant decrease in the number of ectopic beats for patients while on alprenolol in comparison with the number of ectopic beats during the control period ($p < 0.01$) and the placebo period ($p < 0.01$) as shown in Table I but there was no significant difference between the control period and the placebo period ($0.1 < p < 0.2$)

There was no significant difference in mean blood pressure between the control period and the drug period ($0.1 < p < 0.2$) control period and placebo period ($p > 0.5$) or placebo period and drug period ($0.1 < p < 0.2$) as shown in Table II There was no significant difference in systolic or diastolic blood pressure between control period and drug period control period and placebo

Table I Ventricular ectopic beats per minute

Patient	1 Control (average)	2 Placebo (average)	3 Drug (average)	Paired data	
1	9	9	1	1 vs. 2	0 1 < p < 0 2
2	7	13	0	1 vs. 3	p < 0 01
3	22	22	16	2 vs. 3	p < 0 01
4	27	25	13		
5	4	1	0		
6	8	6	1		
7	8	5	1		
8	8	6	0		
9	2	4	4		
10	11	6	0		
11	22	17	11		
12	3	3	0		
13	6	0	4		
Mean ± S D	10 5 ± 7 9	9 0 ± 7 9	5 0 ± 6 5		

Table II Blood pressure

Patient	1 Control (average)		2 Placebo (average)		3 Drug (average)		Paired data	
	B P	Mean	B P	Mean	B P	Mean		
1	118/63	81 3	109/88	95 0	106/80	88 7	1 vs. 2	Mean p > 0 5
2	122/70	87 3	135/67	89 7	125/63	83 7		Systolic p > 0 5
3	122/62	82 0	114/59	77 3	121/58	79 0		Diastolic p > 0 5
4	116/72	86 7	121/82	95 0	123/80	94 3		
5	120/65	83 3	114/63	80 0	108/60	76 0	1 vs. 3	Mean 0 1 < p < 0 2
6	150/86	107 3	136/90	105 3	138/84	102 0		Systolic 0 1 < p < 0
7	156/86	109 3	190/97	129 3	149/89	109 0		Diastolic 0 4 < p < 0 5
8	146/74	98 0	125/73	90 3	122/67	85 3		
9	140/90	106 6	140/78	98 7	160/80	107 7	2 vs. 3	Mean 0 1 < p < 0
10	150/92	111 3	140/85	103 3	140/87	104 7		Systolic 0 4 < p < 0 5
11	128/76	93 3	128/76	93 3	116/78	90 7		Diastolic 0 05 < p < 0 1
12	136/84	101 3	124/87	99 3	130/87	101 3		
13	134/91	105 3	136/73	94 0	133/76	95 0		
Mean ± S.D	96 4 ± 11 2		96 2 ± 12 8		93 6 ± 10 7			
Systolic (average)	133 7		131 7		128 5			
Diastolic (average)	77 8		78 5		78 1			

Table III *Pulse*

Patient	1 Control (average)	2 Placebo (average)	3 Drug (average)	P vs. data	
1	92	85	64	1 vs. 2	$0.02 < p < 0.05$
2	89	91	81	1 vs. 3	$p < 0.01$
3	85	80	81	2 vs. 3	$p < 0.01$
4	91	84	78		
5	77	72	56		
6	97	93	57		
7	76	67	63		
8	85	90	71		
9	55	55	55		
10	96	93	84		
11	83	82	76		
12	111	91	90		
13	120	88	87		
Mean ± S.D.	89.0 ± 16.1	82.0 ± 11.4	74.8 ± 12.0		

period, or placebo period and drug period also shown in Table II.

The pulse showed a significant lowering during the drug period as compared to both the control period ($p < 0.01$) and the placebo period ($p < 0.01$) but no significant lowering when the placebo period was compared to the control period ($0.02 < p < 0.05$) as shown in Table III.

There was no significant effect upon the hematocrit, white blood and differential count, urinalysis serum creatinine, total bilirubin, and serum glutamic pyruvic transaminase by alprenolol. No side effects were experienced by the patients with this dose of drug. Other than the change in ventricular ectopic beats and the lowering of heart rate, there was no significant effect upon the electrocardiogram.

Discussion

The antiarrhythmic action of β-adrenergic blocking agents is felt to be due to either β-adrenergic blockade, a direct depressant (quinidine like) effect, or a combination of both upon the heart. The β-blocking effect occurs at a much lower dosage than the depressant effect. In the dose used in this study (20 mg. every 6 hours) alpreoolol was found to be effective in reducing ventricular ectopic beats. It was also found that, in general, when there was a significant reduction in ventricular ectopic beats, there was a corresponding drop in pulse, but not in systolic, diastolic, or mean blood pressure. Preliminary studies of alprenolol on animals[1] and men at rest showed that in low doses there is a slight beta stimulatory effect upon the heart which is not present with propranolol. This favorable inotropic action appears to account for the lack of drop in blood pressure stroke volume, and cardiac output as mentioned previously. Theoretically, this may be an advantage in that alprenolol appears to have less of a depressant effect upon the heart than propranolol.

The dose of alprenolol employed produced no noticeable side effects and no significant effect upon hemoglobin, white blood and differential count, urinalysis, serum creatinine total bilirubin, and serum glutamic pyruvic transaminase when compared with control and placebo.

Summary

A new β-adrenergic blocking agent, alprenolol, was found to be effective in thirteen patients in a double-blind crossover study comparing its effect in reducing persistent ventricular ectopic beats with that of a placebo. The dose employed (20 mg. every 6 hours orally) did not affect systolic, diastolic, or mean blood pressure but did tend to lower the heart

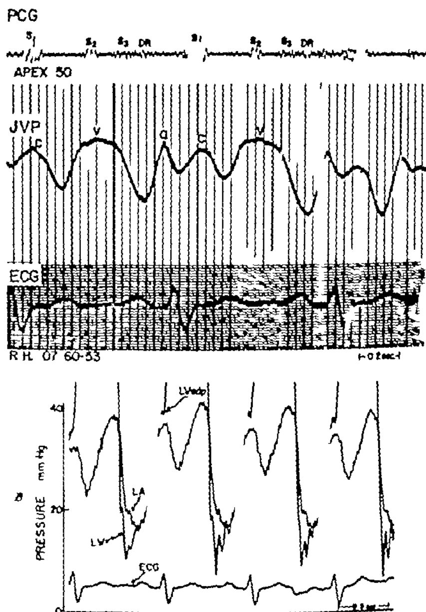


Fig 1 Patient R H (07-60-53) *A* Phonocardiogram (PCG) recorded at cardiac apex at 50 c.p.s. A diastolic rumble is initiated by the third heart sound. *B* Simultaneous direct left atrial and left ventricular pressure tracings. There is an early diastolic pressure gradient between left atrium and left ventricle and a reversed gradient at end diastole. The left ventricular end diastolic pressure is markedly elevated. Abbreviations: *JVP* Jugular venous pulse *DR*, diastolic rumble *LV* left ventricular pressure tracing *LA* left atrial pressure tracing *LVedp* left ventricular end diastolic pressure.

undertaken in order to exclude significant mitral regurgitation

Results

Twelve patients (Group 1 Table 1) were found to have an apical mid-diastolic rumble (Austin Flint murmur) demonstrated by phonocardiogram and auscultation. In the remaining five patients (Group 2) the Austin Flint murmur was judged to be absent by phonocardiogram and auscultation. Auscultation was always performed prior to phonocardiography and an independent assessment of the presence or absence of the murmur was made.

In each patient in Group 1 tracings from simultaneously recorded left ventricular and either left atrial or pulmonary capillary

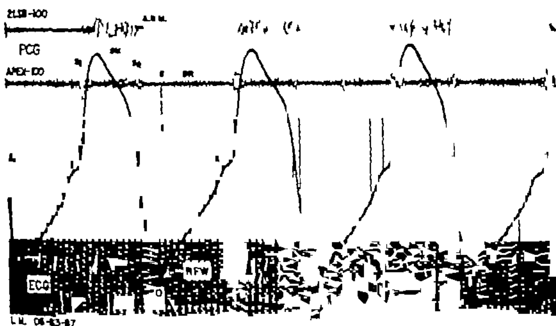


Fig 2 Phonocardiogram and simultaneous apexcardiogram in Patient L. H (06-63-87). Both the murmur of aortic regurgitation and the diastolic rumble are demonstrated. Abbreviations *ARM* Aortic regurgitation murmur; *ACG* apexcardiogram. *RFW* rapid filling wave; *LSB* left sternal border

wedge pressures revealed a typical consistent hemodynamic finding (Fig 1) In every instance there was an early diastolic pressure gradient between left atrium or pulmonary capillary wedge and left ventricle, and there was a reversed and diastolic gradient with left ventricular pressure exceeding left atrial pressure. The early diastolic pressure gradient measured at 0.06 sec. after the beginning of diastole averaged 10.2 mm Hg (range 5 to 25) and at end diastole the left ventricular left atrial reversed gradient averaged 7.5 mm Hg (range 4 to 10) The cardiac index was generally below normal (Table I) Patients in Group 1 had a markedly elevated left ventricular end diastolic pressure and an elevated direct or indirect left atrial mean pressure.

The onset of the Austin Flint murmur generally occurred coincident with a diastolic filling gallop and usually attained maximal intensity at mid diastole The murmur did continue up to the first heart sound, but presystolic accentuation was not obvious in these patients. Uniformly there was a separation between aortic valve closure and the onset of the murmur (Fig 2)

In Group 2 the Austin Flint murmur could not be demonstrated by phonocardiography or auscultation The pressure tracings of patients in Group 2 did not show the early left atrial left ventricular pressure gradient nor the end diastolic reversed gradient (Fig 3) The left ventricular end diastolic pressure was greater than 20 mm Hg in only one patient in this group The brachial arterial pulse pressure was significantly widened in both groups and the degree of aortic regurgitation as assessed by the aortogram was comparable in the two groups. One patient in Group 1 had direct left atrial and left ventricular pressures recorded six months after aortic valve replacement. At the time of restudy the Austin Flint murmur was no longer present and the previously recorded early left atrial left ventricular pressure gradient and reversed end diastolic gradient were absent (Fig. 4)

Discussion

Attention has not been drawn previously to the specific pressure phenomena found in patients with the Austin Flint rumble. However published pressure tracings in patients with severe aortic regurgitation

Table 1 Hemodynamic and phonocardiographic [illegible] of the Austin Flint murmur

Name and unit no.	Sex and age	Etiology	ECG	Mean LA or PCW (mm Hg)	LVEDP (mm Hg)	0.6 sec diastolic LV-LA gradient (mm Hg)	End diastolic LV-LA gradient (mm Hg)	BP (mm Hg)	CI (L/min/M²)
R. H. 07-60-51	M 60	R.H.D.	N.S.R.	[illegible]	[illegible]	6	4	130/61	1.67
R. W. 07-3[illegible]-81	M 50	Unknown	N.S.R.	10 (P.C.W.)	[illegible]	8	8	130/38	1.45
J. K. 06-57-72	M 41	R.H.D.	N.S.R.	18 (P.C.W.)	30	6	6	130/35	2.23
C. S. 07-81-21	M 36	R.H.D.	N.S.R.	16 (P.C.W.)	28	5	5	144/55	2.80
J. H. 06-63-87	M 54	C.M.N.	N.S.R.	10 (P.C.W.)	22	6	6	100/55	1.21
W. B. 07-81-43	M 56	Luet	A.F.	20 (P.C.W.)	24	12	8	180/40	—
L. S. 07-12-51	M 32	R.H.D.	N.S.R.	22 (P.C.W.)	25	12	4	135/34	2.83
J. T. 07-74-32	M 40	R.H.D.	N.S.R.	16 (P.C.W.)	30	8	8	165/40	3.37
S. G. 06-81-86	M 50	S.B.E.	N.S.R.	27 (P.C.W.)	42	25	10	110/45	1.49
J. C. 07-23-10	M 28	R.H.D.	N.S.R.	30 (P.C.W.)	35	16	8	132/50	1.94
G. K. 04-85-39	M 51	R.H.D.	N.S.R.	35 (P.C.W.)	44	8	4	130/50	1.89
J. N. 03-58-13	M 41	R.H.D.	N.S.R.	32 (L.A.)	40	10	8	134/62	2.19
A. R. 07-18-90	F 18	Unknown	N.S.R.	3 (P.C.W.)	9	0	0	193/38	3.38
R. G. 07-28-22	F 26	R.H.D.	N.S.R.	9 (P.C.W.)	20	0	0	124/36	2.67
Z. D. 06-82-30	M 58	S.B.E.	A.F.	20 (L.A.)	15	0	0	200/40	1.95
C. J. 03-86-33	M 26	R.H.D.	N.S.R.	30 (L.A.)	35	0	0	110/38	2.90
J. L. 5-12-78	M 33	R.H.D.	N.S.R.	8 (P.C.W.)	10	0	0	120/38	2.01

[illegible]

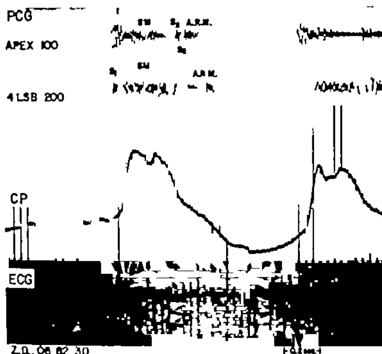


Fig. 3 A Phonocardiogram of Patient Z D (06-82 30) t apex nd left sternal border demonstrating aortic regurgitant murmur and no apical diastolic rumble CP Carotid pulse 1 aorta.

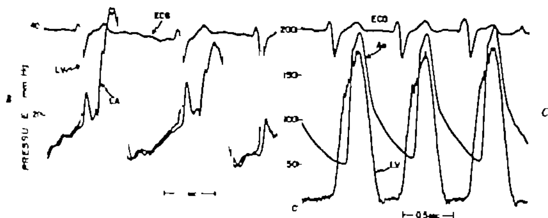


Fig. 3 B Simultaneous direct left trial and left entricular pressure tracings of Patient Z. D (06-82 30) demonstrating neither an early left trial-left entricula pressure gradient nor reversed end diastolic gradient. C. Simultaneous left ventricular and central aortic pulse pressures of P tient Z. D (06-82-30) showing the ide aortic pulse pressure characteristic of severe aortic regurgitation.

appear to show the early diastolic left atrial-left ventricular pressure gradient and the reversed end diastolic gradient From the data obtained in the present study it is likely that there is a direct relationship between the presence of the apical diastolic murmur and the pressure gradient in early and late diastole In the five patients in Group 2 the degree of aortic regurgitation was equally severe to that of patients in Group 1 but neither the murmur nor the pressure gradients were present. In the patient with direct left atrial and left ventricular recordings before and after operation the postoperative examination revealed an absence of both the murmur d the diastolic pressure gradients

The left ventricular

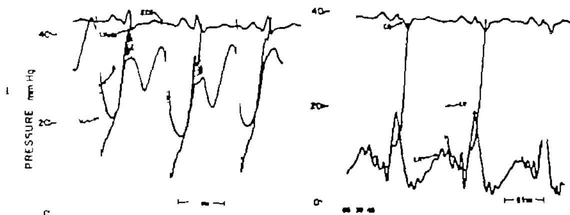


Fig 4 P tient J N (03-38-43). A Preoper tive simultaneous left atrial and left ventricular pressure tracing demonstrating the early left trial-left ve tricular pressure gradient nd reversed end-diastolic pressure gradient B Direct left trial and left ventricula pressure tracings recorded six months postoperatively There is no earl left atrial-left ventricular pressure gradient nor reversed end-diastolic gradient.

sure was markedly elevated in each of the patients with the Austin Flint murmur This finding suggests that when an Austin Fl nt rumble i heard the left ventricular end diast lic pressure will probably be markedly elevated

Although a recent report has emphasized the presystolic component of the Austin Flint murmur the present study again demon trates that the onset of the murmur is in early to mid diastole Indeed defi nite presystolic accentuation of the murmur was not demonstrated n this study

The finding of an early diastolic pressure gradient n a sociation with the murmur stimulates thought concerning its genesis. The generally accepted explanation for the murmur is that it s due to the aortic re gurgitant stream impinging upon the ante rior leaflet of the mitral valve causing the leaflet to vibrate and possibly hindering complete opening of the mitral valve.[9, 10] The finding of the early diastolic gradient in this study i consistent with this widely held explanation Indeed in Patient J K. a yellowi h plaque was observed at opera tio i on the anterior leaflet of the mitral valve and it is likely that the pla que could have resulted from the aorti regurgitant jet It is to be noted that i the patients with the Austin Flint rumble the left atrial pressure was higher than left ventricular pressure early in dia tole but at end dia tole the left ventricular pressure exceeded that in the left atrium This cross-over of pressure gradients in diastole is likely to be a cause of turbulence in the region of the mitral orifice, possibly contributing to the murmur In addition the consistent finding of a reversed gradient at end diastole agrees with other recent observations, and suggests that the presystolic component of the murmur could be due to presystolic mitral regurgitation

An alternate explanation of the observed pressure phenomenon may be related to changes in compliance of the left ventricle subjected to major aortic regurgitation. Stewart and associates[1] recently drew attention to the impaired rate of left ventricular filling in patients with left ventricular hypertrophy secondary to outflow tract obstruction These authors concluded that the rate of left atrial pressure fall after mitral valve opening was reduced probably as a consequence of decreased compliance of the thickened ventricular wall Similarly in patients with severe aortic regurgitation the filling from the left atrium could be hindered by decreased compliance of th left ventricle However it is difficult to explain the presence of a left atrial to left ventricular early diastolic pressure gradient merely a a result of decreased compliance Decreased compliance of the left ventricle leading to marked ele-

vation of left ventricular end diastolic pressure may contribute to the presystolic component of the Austin Flint rumble if this component of the murmur is due to presystolic mitral regurgitation as has been suggested.[8]

It should be emphasized that left ventricular volumes were not measured in the present investigation. Therefore, any speculation concerning the effect of compliance on left ventricular end diastolic pressure needs confirmation through studies of end diastolic ventricular volumes.

Summary

Hemodynamic studies in 12 patients with isolated severe aortic regurgitation and an apical diastolic rumble (Austin Flint murmur) showed a characteristic pressure tracing in diastole. Simultaneously recorded direct or indirect left atrial and left ventricular pressures showed that left atrial pressure was significantly higher than left ventricular pressure in early diastole and that at end diastole the ventricular pressure was higher than atrial pressure. This pressure phenomenon was not observed in five patients with equally severe aortic regurgitation who did not have an apical diastolic rumble. The left ventricular end diastolic pressure was markedly elevated in all 12 patients with the Austin Flint rumble. The possible relationship of these hemodynamic findings to the genesis of the Austin Flint murmur is discussed.

REFERENCES

1. Flint, A.: On cardiac murmurs, Am. J. M. Sc. 44:29, 1862.
2. Segal, J. P., Harvey, W. P., and Corrado, M. A.: The Austin Flint murmur: Its differentiation from the murmur of rheumatic mitral stenosis, Circulation 18:1025, 1958.
3. Kelly, E. R., Morrow, A. G., and Braunwald, E.: Catheterization of the left side of the heart. A key to the solution of some perplexing problems in cardiovascular diagnosis and management, New England J. Med. 262:162, 1960.
4. Meadows, W. R., Van Praagh, S., Indrelka, M., and Sharp, J. T.: Premature mitral valve closure. A hemodynamic explanation for absence of the first sound in aortic insufficiency, Circulation 28:251, 1963.
5. Rees, J. R., Epstein, E. J., Criley, J. M., and Ross, R. S.: Hemodynamic effects of severe aortic regurgitation, Brit. Heart J. 26:412, 1964.
6. Wigle, E. D., and Labrosse, C. J.: Sudden severe aortic insufficiency, Circulation 32:708, 1965.
7. Oliver, G. C., Jr., Gazetopoulos, N., and Deuchar, D. C.: Reversed mitral diastolic gradient in aortic incompetence, Brit. Heart J. 29:239, 1967.
8. Lochaya, S., Igarashi, M., and Shaffer, A. B.: Late diastolic mitral regurgitation secondary to aortic regurgitation: Its relationship to the Austin Flint murmur, Am. Heart J. 74:161, 1967.
9. Herrmann, G. R.: The Austin Flint phenomenon. An experimental and clinical study, Am. Heart J. 1:671, 1926.
10. Gouley, B. A.: The aortic valvular lesions associated with the Austin Flint murmur, Am. Heart J. 22:208, 1941.
11. Stewart, S., Mason, D. T., and Braunwald, E.: Impaired rate of left ventricular filling in idiopathic hypertrophic subaortic stenosis and valvular aortic stenosis, Circulation 37:8, 1968.

Immunologic findings in idiopathic cardiomyopathy*

*T. Frank Camp, M.D.***
*Evelyn V. Hess, M.D.****
*Gene Conway, M.D.***
*Noble O. Fowler, M.D.******
Cincinnati, Ohio

Idiopathic cardiomyopathy (primary myocardial disease) is a not uncommon variety of heart disease. In 1961 we reported an autopsy study of 18 patients with idiopathic cardiomyopathy observed within a period of a few years at the University of Cincinnati Medical Center. In this institution we continue to witness several autopsies each year of patients with this disorder, and it is not uncommon to have four or more patients simultaneously in the hospital with congestive heart failure caused by cardiomyopathy.[1,2] Segal and associates established a clinic at Georgetown University for patients with cardiomyopathy with more than 200 patients in attendance. In their patients, idiopathic cardiomyopathy was approximately three times as common as cardiomyopathy of known cause. Alexander[4] recently described a group of 100 patients, mostly believed to have alcoholic cardiomyopathy, collected in a 14 year period at the Minneapolis Veterans Hospital. In his experience, myocardial disease was responsible for 2.4 per cent of all varieties of heart disease.

As implied by the name, the etiology of idiopathic cardiomyopathy is unknown. In recent years, attention has been directed to several possible causes.[1] Principal among these are alcoholism,[illegible] infectious disease, especially viral infections,[illegible] familial disease,[illegible] dietary deficiency,[illegible] and autoimmune disease.[illegible]

The present study was undertaken to evaluate serologic evidence of possible immune mechanisms including heart muscle antibodies in a group of patients with idiopathic cardiomyopathy.

Materials and methods

Selection of patients. The diagnosis of idiopathic cardiomyopathy must be made by exclusion of other varieties of heart disease. The following clinical criteria were

From the Divisions of Cardiology and Immunology, Department of Internal Medicine, University of Cincinnati College of Medicine and Veterans Administration Hospital, Cincinnati, Ohio.
Supported by United States Public Health Service Grants HE-[illegible] and HE [illegible].
Received for publication Aug. 14, 1966.
*Initial results presented at the Thirty-ninth Scientific Sessions of the American Heart Association, 1966.
**Fellow in Cardiology, University of Cincinnati College of Medicine.
***Senior Investigator, The Arthritis Foundation; Associate Professor of Medicine, University of Cincinnati College of Medicine; Director of Division of Immunology, Cincinnati General Hospital.
****Associate Professor of Medicine, University of Cincinnati College of Medicine; Chief of Cardiology Section, Veterans Administration Hospital.
*****Professor of Medicine, University of Cincinnati College of Medicine; Director of Cardiac Research Laboratory, Cincinnati General Hospital.

used for inclusion of a patient in this group Each demonstrated cardiac enlargement by radiologic study or had evidence of left or right ventricular hypertrophy by physical examination during some part of his clinical course. Each patient had either a ventricular or atrial gallop, or a summation gallop during periods of congestive heart failure. Each patient had an abnormal electrocardiogram (ECG) No patient was included who had a history of angina pectoris, myocardial infarction or electrocardiographic evidence of previous myocardial infarction. Patients with a sustained blood pressure of 150/100 mm. Hg or more were considered to have hypertensive cardiovascular disease and were not included in this study A diastolic cardiac murmur valvular calcification diabetes mellitus, hypercholesterolemia or hyperthyroidism excluded patients from this study No patients had evidence of idiopathic hypertrophic subaortic stenosis. Twenty-eight patients satisfied the above criteria for the diagnosis of cardiomyopathy Their ages were from 17 to 60 years. There were 16 men and 12 women 19 of the patients were Negro and 9 were Caucasian Five additional patients satisfied most but not all of the above criteria and were classified as probable idiopathic cardiomyopathy These patients had definite heart disease without discernible etiology Two lacked clinical evidence of left ventricular enlargement one had toxic hepatitis one had postprandial hyperglycemia and one had slight hypercholesteremia However all had a history of congestive heart failure accompanied by gallop rhythm and all had abnormal ECG s.

Thirteen of the 28 patients with cardiomyopathy were studied within 3 months of the onset of symptoms. Of these 13 patients 4 had an acute febrile illness followed by protracted cardiac enlargement or congestive failure three of these had associated pericarditis. In one the illness was initiated by atrial fibrillation in one pulmonary embolism was the first evidence of disease. One patient was examined when the illness began with a skin rash and generalized edema following the use of hair dye evidence of heart failure appeared four weeks later In 6 of the 13 patients, the initial manifestations were acute dyspnea and gallop rhythm with roentgen evidence of cardiac enlargement Three of these patients had normal chest x-rays without evidence of cardiac enlargement at respective periods of 3 weeks, 12 months, and 15 months prior to the onset of heart failure Another had a normal ECG and clinical examination 3 months prior to the onset of failure The remaining two were not examined during the 2 year period prior to the onset of heart failure

Four other groups of patients were studied (1) Twelve had a variety of heart diseases. (2) Six others had miscellaneous systemic diseases often associated with increased globulin They were included to give information on the specificity of results in the cardiomyopathy group. (3) Five patients with active systemic lupus erythematosus had cardiac involvement (4) Twenty five normal subjects between the ages of 18 and 50 years served as controls. Normal subjects were in apparent good health and comprised a group of physicians medical students, technicians, and older children from an orphanage The different disease groups are listed in Table I and are further categorized in Tables II and III Patients were studied at the Cincinnati General Hospital and Cincinnati Veterans Administration Hospital Serum was stored at −20° C

Heart tissue Samples of right ventricular muscle were obtained from a child with tetralogy of Fallot during cardiac surgery These were quick frozen and stored at −40° C This tissue was first tested with known positive and negative sera before being used in this study

Antigammaglobulin conjugate A rabbit antiserum to human immunoglobulins G A and M was conjugated with fluorescein isothiocyanate by the method described by Hess and associates.

Staining procedure Tissue sections were cut at 4 μ in a cryostat thawed on a slide and fixed in acetone for 10 minutes at room temperature The sections were then air dried and given a final rinse in buffered saline Test serum was applied to the sections for one hour in a moist chamber the slides were then washed for 10 minutes in three changes of buffered saline and incubated with the conjugated antihuman gamma globulin for another hour in the

Table I Heart mu cle antibodies in various conditions

C tegor	N individuals	SS-IMF stain g No	SS-IMF stain g %	D f se sta g N	D f se sta g %	Total positive staining No	Total positive staining %
Id pathic cardiom opathy	28	2	7	1	3 6	3	10 7
I able idiopathic cardiom opathy	5	0	0	1	20	1	20
M s llaneou cardiac disease	12	3	25	2	17	4	33
Miscellaneous d seases	6	3	50	0	0	3	50
S t mic lupu erythematosus	5	0	0	0	0	0	0
N rmal ndividuals	25	0	0	1	4	1	4

* ent in this grou had both SS-IMF and diff se staining.

Table II Heart muscle antibodies in miscellaneous cardiac diseases

T pe of d se se	No patients	No. with positive staining: SS-IMF	No. with positive staining: D fuse
H p l nd s	3	1	0
I ndrome	2	0	0
H t d nd congestive h rt	2	1	0
h m d tis	1	0	0
rd l infarction ndrome	1	0	0
H pe t rd ov scula disease	1	0	1
ler c h rt dise se nd ba b terial endocarditis	1	1	1
b cterial nd card tis	1	0	0

moist han ber Th slides were again wa hed for 10 minutes in three changes of buffered saline drained and the sections mounted in buffered glycerol

Readings The slides were examined with an American Optical Fluorostar micro-scope equipped with an Osram HBO 200 mercury lamp 2 mm Corning 5840 filter and a red-excluding BG 14 filter The slides were re d independently by two observers without knowledge of the source of the serum being tested The degree of fluorescence was graded on a 0 to 4+ scale 2+ fluorescence being required for a positive reading This standard was adopted when experience showed that ± to 1+ degrees of fluorescence were difficult to interpret consistently The sera were retested at a later date at least once and were retested twice in many instances A previous study showed that the result of this method were consistent in 97 per cent of 1 287 slides examined representing the sera of 624 individuals. Disagreement was principally in distinguishing between 1+ and 2+ fluorescence. There was com-plete agreement with regard to all negative interpretations

Other serological tests The following pro-cedures were performed on the 81 sera tested for heart muscle antibodies (1) rheumatoid factor b the latex fixation test (Hyland slide test) and sensitized sheep cell agglutination test (SSCAT) ( ) standard test for syphilis (Wassermann reaction VDRL, Kahn) (3) total serum proteins with albumin-globulin ratio and serum immunoelectrophoresis (4) thyroid

Table III. *Heart muscle antibodies in miscellaneous disease states*

Disease	*No. patients*	*No. with positive staining*	
		SS-IMF	*Diffuse*
Chronic hepatitis	1	1	0
Postnecrotic cirrhosis and active hepatitis	1	1	0
Polymyalgia rheumatica	1	0	0
Polymyositis	1	0	0
Rheumatoid arthritis	1	1	0
Rheumatoid arthritis, myasthenia gravis, and surgically treated Graves' disease	1	0	0

antibodies by the thyroglobulin agglutination test (Hyland slide test) and indirect immunofluorescent test for microsomal antibodies[17] (5) antinuclear factor test by indirect immunofluorescent test on infant thyroid.[17]

Results

1. *Heart muscle antibodies.* Three distinct patterns of myocardial staining have been previously reported[17] and were observed in this study. These were sarcolemmal-subsarcolemmal (SS), intermyofibrillar (IMF) and diffuse (D). Staining of the nucleus was noted only in those patients with systemic lupus erythematosus.

CARDIOMYOPATHY. Of the 28 patients with cardiomyopathy, demonstrated SS-IMF staining and 1 diffuse myocardial staining (Table I). Of the 5 patients with probable cardiomyopathy, 1 demonstrated myocardial staining of the diffuse pattern. This patient had toxic hepatitis in addition to heart disease.

MISCELLANEOUS CARDIAC DISEASE. Of the 11 patients with miscellaneous cardiac disease, 2 had positive SS-IMF staining, 1 had diffuse, and 1 had both patterns (Table I). One of these patients had idiopathic pericarditis, one had congestive heart failure associated with hyperthyroidism, 1 had hypertensive cardiovascular disease, and 1 had subacute bacterial endocarditis associated with arteriosclerotic heart disease (Table II).

MISCELLANEOUS DISEASE. Six patients had a variety of miscellaneous diseases though none had heart disease. Three of the group demonstrated SS-IMF staining (Table I). Two patients with positive staining had liver disease. The most marked SS-IMF staining in the entire study of 81 patients was noted in this group in a patient with postnecrotic cirrhosis and active hepatitis. One patient with rheumatoid arthritis had positive SS-IMF staining (Table III).

SYSTEMIC LUPUS ERYTHEMATOSUS. There were 5 patients with this disease. None of them demonstrated SS-IMF or diffuse staining (Table I). Four of the 5 had a positive antinuclear factor test.

2. *Serum proteins.* The serum globulin exceeded 3.5 Gm. per cent in 4 of the 28 cardiomyopathy patients and in 1 of the probable group. Tables IV and V show the relationship between the globulin level and the other variables tested. Two of the 4 patients had heart antibodies, one the diffuse pattern and one the SS-IMF pattern.

IMMUNOELECTROPHORESIS. IgG was moderately increased in the sera of 3 of 28 patients with definite cardiomyopathy and in one of 5 with probable cardiomyopathy (Table VI). IgA was moderately *increased* in the sera of 7 patients and markedly increased in [illegible] with definite cardiomyopathy. One patient with probable cardiomyopathy demonstrated a moderate increase of IgA. IgM was within the normal range in the 2 groups. Serum haptoglobin was moderately *increased* in the sera of

Table IX. Abnormal serum factors in cardiomyopathy

Form of cardiomyopathy	No. individuals	Serum global >3.5 Gm./100 ml.	Abnormal I.E.P.A.	+ Latex	+ VDRL	+ A.N.F.	+ Thyroid antibodies
Definite cardiomyopathy	28	4	8 (↑ IgA)	4	2	0	1
Probable cardiomyopathy	5	1	1 (↑ IgA)	0	0	0	0

Table X. Individual correlations in cardiomyopathy

Patient	Heart antibody	Serum globulin Gm./100 ml. serum	I.E.P.A.	Latex test	VDRL	A.N.F.	Thyroid antibodies
B. W.	+ (SS-IMF)	4.2	IgG++ IgA++	0	0	0	0
R. F.	+ (SS-IMF)	3.0	IgA++	0	0	0	0
W. B.	+ (D)	2.5	IgA++	0	+	0	0
J. M.	+ (D)	4.1	IgG++ IgA++	0	0	0	0

*Table XI. Immunoelectrophoresis in idiopathic cardiomyopathy**

	IgG	IgA	IgM	Haptoglobin	Orosomucoid	β (Related to third component of complement)
Slight increase	10	5	1	7	7	
Moderate increase	3	7		6	1	
Decrease	1	2	1	5		1
Slight increase	1	1	1			
Moderate increase	1	1		1	1	
Decrease			1			

*The data above the line apply to the 28 patients with definite cardiomyopathy. The data below the line apply to the 5 patients with probable cardiomyopathy.

6 patients and markedly decreased in 1 with cardiomyopathy. Serum complement was normal except in one patient with cardiomyopathy where it was slightly reduced. This patient had a positive diffuse staining pattern.

All 4 cardiomyopathy patients with heart muscle antibodies had increased IgA (Table X).

3. *Rheumatoid factor tests.* Latex fixation tests were performed on all sera studied. Four positive tests were found (Table IX). The sensitized sheep cell agglutination test (SSCAT) was negative on these sera. None of these patients had heart antibodies.

4. *Serologic tests for syphilis.* Biologic false positive tests for syphilis are recognized as one of the hallmarks of abnormal immunological phenomena.[14] VDRL determinations were therefore obtained on all patients with cardiomyopathy. Negative reactions were obtained on all sera except in one patient who had a positive Reiter protein and T.P.I. tests.

5. *Antinuclear factor tests.* These tests were uniformly negative in the cardiomyopathy groups.

6. *Thyroid antibodies.* One patient with definite cardiomyopathy had a positive thyroglobulin reaction.

Discussion

These immunologic studies of 33 patients with idiopathic cardiomyopathy do not support the concept that immunologic mechanisms are responsible in the major ity of instances. Evidence of heart muscle antibodies was found in only 12 per cent, more often than in normal subjects (4 per cent in this study) but less often than in patients with miscellaneous cardiac disease (33 per cent) or in a previous study of patients with acute rheumatic fever and carditis (63 4 per cent) [17] Similar results were given in a report of a study of pa tients with primary myocardial disease by Fletcher and Wenger [58] However van der Geld and associates[38] found heart antibody globulins in a higher percentage of patients with cardiomegaly of unknown origin Heart muscle antibodies were present in 53 per cent of 43 patients with endomyocardial fibrosis and in 35 per cent of 31 with idiopathic cardiomegaly Sanders and Ritts[21] found bound gamma globulin in the ventricular muscle in 5 of 9 patients with idiopathic disease of the myocardium and positive tests for antimyocardial globulins were found in 20 per cent of cardiomyopathy patients by Robinson and coworkers.[40] The high incidence of anti heart antibodies in patients with miscellaneous cardiac diseases in our study (4 of 12) de serves comment Van der Geld[22] found anti-heart antibodies in 13 of 15 instances of post-pericardiotomy syndrome and in 8 of 14 patients with postmyocardial in farction syndrome Seventeen of 62 pa tients with various heart diseases including myocardial infarction had positive tests. The results suggest that the release of cardiac antigen by various forms of injury including trauma ischemia, and infection may stimulate the production of anti heart antibodies.

Negative studies for antimyocardial globulins might be found in a group of patients believed to have cardiomyopathy if many of them actually had coronary artery disease as the cause of cardiac enlargement. We believe that our criteria for the diagnosis of idiopathic cardiomyopathy as shown by previous experience with similar patients followed to autopsy would permit the inclusion of only a small percentage of patients with coronary artery disease Further only 3 of the 33 patients in our study were men over 40 years of age so that silent coronary artery disease was statistically unlikely in our study group One of these 3 men has been autopsied and the diagnosis of idiopathic cardiomyopathy confirmed

Negative studies for antimyocardial globulins in patients with cardiomyopathy might be found because considerable time had elapsed between the onset of disease and the time of serum study Hess and associates[17] found heart muscle antibodies in 63 4 per cent of patients with acute rheumatic carditis but in only 18 5 per cent of patients with inactive rheumatic heart disease In our patients, the serum for study was obtained during the acute illness or within 3 months of the onset of symptoms in 13 of 28 patients. In none of these 13 patients was the immunofluorescent study for heart antibody positive. False positive tests might occur in liver disease In our cardiomyopathy patients, with one exception there was no evidence of liver disease or other systemic illness serum albumin levels were above 3 Gm per 100 ml plasma in 28 of the 33 Hyperglobulinemia may result from heart failure if there is hepatic congestion and was reported in 51 per cent of such patients in one study [22] and in 18 of 43 patients with right ventricular failure in another study [43] However only 5 of our 33 cardiomyopathy patients had hyperglobulinemia and only 4 had moderate increase of gamma globulin perhaps reflecting a less advanced state of cardiac decompensation and liver congestion

Other studies which might have been positive in some varieties of autoimmune disease were normal or negative in our patients with cardiomyopathy These were beta 1c globulin (related to third component of complement) negative sheep cell agglutination tests and infrequently positive latex tests. The patient with a positive serologic test for syphilis had a positive T P I test, and thus presumably had had syphilis and was not an example of a biologic false positive test for syphilis. Increased values for serum haptoglobin may be expected as a nonspecific reaction to tissue necrosis, inflammation thrombosis or proliferation [44,45] Decreased levels of

beta 1c globulin might have been expected if complement-fixing antigen antibody complexes were active. Reduced levels also occur in hepatic disease and acute systemic lupus erythematosus.[34] The moderately increased values of IgG and IgA in some patients are probably nonspecific reactions, common in chronic illness.[34] Two of the 9 patients with increased IgA had heart muscle antibodies. In heart failure alone, study of serum proteins by electrophoresis shows a modest increase of alpha 2 globulin but not of beta or gamma globulin.[34] The normal or slightly elevated levels of orosomucoid, a seromucoid, are in keeping with the absence of parenchymal liver disease[34] and do not speak for a striking inflammatory process, which should cause a greater increase.

Mackay and Burnet[34] listed characteristics of autoimmune conditions. These include plasma gamma globulin levels above 1.5 Gm. per 100 ml. serum, auto-antibody against a body component, deposition of denatured gamma globulin at sites of election, accumulation of lymphocytes and plasma cells in damaged tissue, therapeutic benefit from steroid therapy, and often more than one autoimmune lesion in the same individual. Most studies of patients with autoimmune disease demonstrate a female sex preponderance. Patients with cardiomyopathy tend to be equally divided between the sexes. In the present group men outnumbered women. There is usually little evidence of pericarditis or myocardial infiltration with lymphocytes in patients with cardiomyopathy. Although occasionally present, these latter two features are usually absent in histologic studies of the heart of patients with cardiomyopathy in our experience and in that of others.[17]

In our patients and in those investigated by Fletcher and Wenger[20] it appears that immunologic mechanisms were unlikely to be responsible for the majority of instances of cardiomyopathy. Serial studies of a larger number of patients during the first few weeks of the acute illness might be desirable. We made a second study for anti-heart antibodies after an interval of a few weeks in two of our patients thus far and the results were negative in each instance. Alcohol was believed to be the cause of myocardial disease in 83 per cent of Alexander's patients[4,5] but his criteria for the diagnosis of alcoholism were not stringent. In our autopsied patients with cardiomyopathy approximately one third were alcoholics,[1] but a cause-and-effect relationship was not proved. Evidence of viral infection is lacking in some studies of patients with cardiomyopathy[11,12] but it is present in a few instances.[13,14,15] A family history of similar disease is found in a relatively small percentage of patients with nonobstructive cardiomyopathy; such a history was present in only 3 of approximately 40 autopsied patients whom we have studied. In obstructive cardiomyopathy, a positive family history is much more common, being present in 23 of 64 patients reported by Braunwald and associates.[17] It appears that there is a considerable percentage of patients with cardiomyopathy in whom the disease is not obviously related to alcohol, heredity, infection, or immune mechanisms, and further etiologic investigation remains to be done in this group.

Summary

Thirty-three patients with idiopathic cardiomyopathy were studied for evidence of autoimmune disease. Three additional groups of patients were investigated: 12 with other cardiac diseases, 11 with miscellaneous systemic diseases. 75 normal subjects served as controls. Heart muscle antibodies were found in 4 patients with cardiomyopathy (12 per cent), more often than in controls (4 per cent), but less often than in patients with other cardiac diseases (33⅓ per cent). None showed evidence of an antinuclear factor. Total serum globulins exceeded 3.5 Gm. per 100 ml. serum in 5 of 33 cardiomyopathy patients. By immunoelectrophoresis, IgA was increased in 9 of 33 cardiomyopathy patients. IgG was elevated in 4 of the 33 patients. Serum complement levels were normal in the cardiomyopathy group; none had a biologic false positive test for syphilis. Although 4 had a positive latex test for the rheumatoid factor, none had a positive sheep cell agglutination test.

These results fail to show evidence of autoimmune disease in the majority of our patients with idiopathic cardiomyopathy and do not support the concept that im-

mune mechanisms are responsible for this disease in the majority of instances.

The immunoelectrophoretic studies in this investigation were made in the laboratory of Dr. Clark West, Cincinnati Children Hospital. We wish to thank Miss M. J. Heimbrock for her valuable technical assistance.

REFERENCES

1. Fowler, N. O., Gueron, M., and Rowlands, D. T., Jr.: Primary myocardial disease, Circulation 23:498, 1961.
2. Fowler, N. O., and Gueron, M.: Primary myocardial disease, Circulation 32:830, 1965.
3. Fowler, N. O.: Classification and differential diagnosis of the myocardiopathies, Progr. Cardiovas. Dis. 7:1, 1964.
4. Segal, J. P., Harvey, W. P., and Gurel, T.: Diagnosis and treatment of primary myocardial disease, Circulation 32:837, 1965.
5. Alexander, C. S.: Idiopathic heart disease. I. Analysis of 100 cases, with special reference to chronic alcoholism, Am. J. Med. 41:213, 1966.
6. Alexander, C. S.: Idiopathic heart disease. II. Electron microscopic examination of myocardial biopsy specimens in alcoholic heart disease, Am. J. Med. 41:229, 1966.
7. Brigden, W.: Uncommon myocardial disease: the non-coronary cardiomyopathies, Lancet 2:1179, 1243, 1957.
8. Dye, C. L., Rosenbaum, D., Lowe, J. C., Behnke, R. H., and Genovese, P. D.: Primary myocardial disease. I. Clinical features, Ann. Int. Med. 58:426, 1963.
9. Evans, W.: Alcoholic cardiomyopathy, Am. Heart J. 61:556, 1961.
10. Regan, T. J., Moschos, C. B., and Hellems, H. K.: Ethanol-induced alteration of myocardial metabolism and function (P), Circulation 28:788, 1963.
11. Burch, G. E., and Walsh, J. J.: Cardiac insufficiency in chronic alcoholism, Am. J. Cardiol. 6:864, 1960.
12. Wendt, V. E., Wu, C., Balcon, R., Doty, G., and Bing, R. J.: Hemodynamic and metabolic effects of chronic alcoholism in man, Am. J. Cardiol. 15:175, 1965.
13. Medical News: J. A. M. A. 197:27, No. 4, July 1966.
14. Wendt, V. E., Ajluni, R., Bruce, T. A., Prasad, A. S., and Bing, R. J.: Acute effects of alcohol on the human myocardium, Am. J. Cardiol. 17:804, 1966.
15. Sanzo, P. B., and Meister, H. P.: Alcoholic myocardiopathy, Am. J. Clin. Path. 39:294, 1963. (Abst.)
16. Ellner, M. J., and Gamsiracusa, F. J.: Heart and alcohol, California Med. 84:234, 1956.
17. Tobin, J. R., Jr., Driscoll, J. F., Lim, M. T., Sutton, G. C., Szanto, P. B., and Gunnar, R. M.: Primary myocardial disease and alcoholism. The clinical manifestations and course of the disease in a selected population of patients observed for three or more years, Circulation 35:754, 1967.
18. Woodward, T. E., McCrumb, F. R., Jr., Carey, T. N., and Togo, Y.: Viral and rickettsial causes of cardiac disease including the Coxsackie virus etiology of pericarditis and myocarditis, Ann. Int. Med. 53:1130, 1960.
19. Sanders, V.: Idiopathic disease of myocardium. A prospective study, Arch. Int. Med. 112:661, 1963.
20. Hibbs, R. G., Ferrans, V. J., Black, W. C., Walsh, J. J., and Burch, G. E.: Virus-like particles in the heart of a patient with cardiomyopathy. An electron microscopic and histochemical study, Am. Heart J. 69:327, 1965.
21. Abelmann, W. H.: Current concepts: myocarditis, New England J. Med. 275:832, 944, 1966.
22. Bainbridge, M. V., Darracott, S., Chayen, J., Bitensky, L., and Poulter, L. W.: Possibility of a new infective aetiological agent in congestive cardiomyopathy, Lancet 1:171, 1967.
23. Kurz, H., Sainai, G., Krimpotic, E., and Slodki, S.: Cardiovascular manifestations of proven Coxsackie infections, Am. Coll. Physicians Prog. Forty-eighth Annual Session, p. 39, 1967.
24. DePasquale, N. P., Burch, G. E., Sun, S. C., Hale, A. R., and Mogabgab, W. J.: Experimental Coxsackie virus B-4 valvulitis in cynomolgus monkey, Am. Heart J. 71:678, 1966.
25. Fletcher, G. F., and Wenger, N. K.: Autoimmune studies in patients with primary myocardial disease, Circulation 37:1032, 1968.
26. Harris, L. C., Nghiem, Q. X., Schreiber, M. H., and Wallace, J. M.: Severe pulsus alternans associated with primary myocardial disease in children. Observations on clinical features, hemodynamic findings, mechanism, and prognosis, Circulation 34:948, 1966.
27. Nasser, W. K., Williams, J. F., Mishkin, M. E., Childress, R. H., Helmen, C., Merritt, A. D., and Genovese, P. D.: Familial myocardial disease with and without obstruction to left ventricular outflow: clinical, hemodynamic, and angiographic findings, Circulation 35:638, 1967.
28. Paré, J. A. P., Fraser, R. G., Pirozynski, W. J., Shanks, J. A., and Stubington, D.: Hereditary cardiovascular dysplasia: a form of familial cardiomyopathy, Am. J. Med. 31:37, 1961.
29. Davies, L. G.: A familial heart disease, Brit. Heart J. 14:206, 1952.
30. Walther, R. J., Madoff, I. M., and Zinner, K.: Cardiomegaly of unknown cause occurring in family: report of three siblings and review of the literature, New England J. Med. 263:1104, 1960.
31. Braunwald, E., and Aygen, M. M.: Idiopathic myocardial hypertrophy without congestive heart failure or obstruction to blood flow. Clinical, hemodynamic, and angiographic studies in fourteen patients, Am. J. Med. 35:7, 1963.
32. McKusick, V. A.: Genetical view of cardiovascular disease (Lewis A. Conner memorial lecture), Circulation 30:326, 1964.
33. Weber, D. J., Gould, L., and Schaffer, A. I.: Family with idiopathic myocardial hypertrophy, Am. J. Cardiol. 1:419, 1966.
34. Gillanders, A. D.: Nutritional heart disease, Brit. Heart J. 13:177, 1951.
35. Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Austin, R. S.: Occidental beriberi heart disease, J. A. M. A. 131:717, 1946.

36. Akbarian M Yannopoulos, N A and Abelmann W H Hemodynamic studies in beriberi heart disease Am. J Med. 41 197 1966
37. Schlesinger P and Benchimol A. B Cardiac beriberi simulating arteriosclerotic heart disease Am Heart J 42:801 1951
38. Higginson J Gillanders, A. D and Murray J F The heart in chronic malnutrition, Brit. Heart J 14:213 1952
39. Wuhrmann F Myocardosis, Zurich, Benno Schwabe 1956
40. Griffith R L Condition of the heart following beriberi and malnutrition Arch. Int. Med 89 743 1952
41. Smythe P M Swanepoel, A and Campbell J A H The heart in Kwashiorkor Brit Med. J 1:6 1962
42. Sanders, V and Ritt R. E Jr Ventricular localization of bound gamma globulins in idiopathic disease of the myocardium J A. M A 191:59 1965
43. Robinson, J Anderson T and Grieble H Serologic anomalies in idiopathic myocardial disease Clin Res 14 335 1966
44. MacKay I R and Burnet F M Autoimmune disease Springfield Ill 1963 Charles C Thomas Publisher pp 1 17
45. Letters to the Editor Lancet 1:48, 1966
46. Van der Geld H [illegible] F Somers, K and Ka[illegible] B R Immunohistological and serologic [illegible] endomyocardial fibrosis, Lancet 1 10 1966
47. Hess [illegible] W Taranta, A. and [illegible] Heart muscle antibodies in rheumatic [illegible] the disease J Clin Invest. 43:886 1964
48. [illegible] M B[illegible] J Lospalluto J Badin, J and M[illegible] C Agglutination and inhibition by serum globulin in the sensitized sheep cell agglutination reaction in rheumatoid arthritis, Am. J Med 20:500 1956.
49. Balfour B. M Doniach, D Roitt I. M and Couchman, K. G.: Fluorescent antibody studies in human thyroiditis. Autoantibodies to an antigen of the thyroid colloid distinct from thyroglobulin Brit J Exper Pathol. 42:307 1961
50. Harvey A. M : Auto-immune disease and the chronic biologic false-positive test for syphilis, J A M A. 182:513 1962.
51. Van der Geld H Anti-heart antibodies in the post pericardiotomy and the post-myocardial infarction syndromes, Lancet 2:617 1964
52. Richman, S. M Delman, A. J and Grob, D Alterations in indices of liver function in congestive heart failure with particular reference to serum enzymes, Am. J Med 30:211 1961.
53. Sherlock, S. The liver in heart failure. Relation of anatomical functional and circulation changes, Brit. Heart J 13:273 1951
54. Nyman M Serum haptoglobin. Methodological and clinical studies, Scandinav J Clin & Lab. Invest Suppl. 39 1 1959
55. West, C. D and Hong, R. The glycoproteins of serum, J Pediat 60:430 1962.
56. Sunderman, F W Jr and Sunderman, F W Clinical applications of the fractionation of serum proteins by paper electrophoresis, Am J Clin. Path 27 125 1957
57. Braunwald, E., Lambrew C. T Rockoff S D Ross, J J and Morrow A. G. Idiopathic hypertrophic subaortic stenosis I A description of the disease based upon an analysis of 64 patients, Circulation 30 (Suppl IV) 3, 119, 1964

Arrhythmias induced by pacemaking on demand

Ruth C. Spritzer, M.D.
Ephraim Donoso, M.D.
Howard L. Gadboys, M.D.
Charles K. Friedberg, M.D.
New York, N. Y.

Increasing use of demand pacemakers has provided an opportunity to observe new disorders of rhythm due to these devices. In 1967 Castellanos and associates[1] described an arrhythmia which they termed iatrogenic escape-capture bigeminy. In a patient with a demand pacemaker. The present communication illustrates a variety of arrhythmias appearing in 9 patients after nonsynchronous demand pacemaker implantation. Five demand pacemaker-induced arrhythmias are presented. These include escape-capture bigeminy produced by a different mechanism from that previously described, pacemaker ventriculophasic sinus arrhythmia, trigeminy, post-extrasystolic pacemaker escape, and the concertina effect.

The reported arrhythmias occurred in 9 of the first 16 patients in whom permanent asynchronous demand pacemakers were inserted at the Mount Sinai Hospital. All of the patients were asymptomatic when the arrhythmia was recorded. The electrocardiograms (ECG's) of the remaining 7 patients showed either a conducted supraventricular rhythm or complete or sporadic ventricular capture by the nonsynchronous demand pacemaker.

Clinical features

The pertinent data on the 9 patients with unusual arrhythmias after pacemaker implantation are summarized in Table I.

Four females and 5 males, ranging in age from 47 to 87 years, are included in the study. Evidence of arteriosclerotic, hypertensive, or rheumatic heart disease was present in 5 of the 9 patients. Of the 4 patients without heart disease, 1 had hypothyroidism.

The pacemaker was inserted because of dizziness with or without frank syncope and abnormal ECG's which indicated that the symptoms were probably due to excessive slowing or failure of the natural pacemaker. ECG's were obtained prior to the insertion of a pacemaker in 3 patients during dizziness. In 1 of these, the ECG showed regular sinus rhythm with a 2:1 A-V block and a ventricular rate of 33 beats per minute. When the patient was asymptomatic, the ECG showed sinus bradycardia with a ventricular rate of 50 beats per minute and a right bundle branch block pattern. In a second, the ECG during dizziness showed sinus bradycardia with a rate of 30 beats per minute. ECG's taken when the patient was asymptomatic showed sinus brady

From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, N. Y. 10029.
This investigation was supported in part by Grants HE-094 6-09, HE 3240-09, and HE-12620-02 from the National Institutes of Health, United States Public Health Service.
Received for publication Aug. 28, 1968.
Work was done while Dr. Spritzer held a postdoctoral fellowship from the United States Public Health Service.
Vol. 77, No. 5, pp. 619-627, May, 1969

cardia with a rate of 40 to 50 beats per minute In a third the ECG during dizziness showed atrial flutter with advanced heart block and a ventricular rate of 50 beats per minute The patient was asymptomatic when the ventricular rate was 60 beats per minute Six patients did not have ECGs recorded while experiencing dizziness. Their usual ECGs showed either sinus bradycardia or regular sinus rhythm with a pattern suggestive of bilateral bundle branch block All patients showed evidence of supraventricular conduction

The demand pacemaker

The Chardack-Greatbatch (Medtronic 5841) implantable transvenous demand pacemaker was set to pace at a usual rate of 62 beats per minute (range 56 to 72 beats per minute) This instrument functions by sensing a two millivolt deflection of the preceding R wave and allowing artefactual stimulation only when the preset rate of the artificial pacemaker exceeds that of the natural pacemaker The demand pacemaker [illegible] for a single beat or a series of [illegible] depending on the rate of the natural pacemaker

The [illegible] graphic description of [illegible] arrhythmias is facilitated [illegible] analogies with naturally occurring phenomena The demand pacemaker generator which initiates impulses at a preset rate has as its naturally occurring analogue a subsidiary junctional or ventricular pacemaker The demand pacemaker-sensing circuit detects spontaneous ventricular depolarization as does the subsidiary pacemaker in the absence of entrance block When spontaneous depolarization occurs and is detected by the sensing circuit a new pacer cycle is begun just as the junctional or ventricular pacemaker has its firing cycle reset by antecedent ventricular depolarization Thus, the demand pacemaker escape mechanism simulates the natural escape mechanism which may occur in sinus bradycardia sinus arrhythmia sinoatrial block sinus arrest A V block, and during the delay in ventricular activation following a premature systole

The arrhythmia described in this communication may readily be compared with naturally occurring phenomena Thus, pacemaker escape-capture bigeminy simulates a subsidiary pacemaker escape followed by a supraventricular capture pacemaker trigeminy is analogous to a supraventricular beat followed by two subsidiary pacemaker escape beats, or by a fusion beat and a subsidiary pacemaker beat post-extrasystolic pacemaker escape simulates a post-extrasystolic escape by a secondary pacemaker Pacemaker fusion beats simulate fusion between a conducted supraventricular beat and an escaping ventricular pacemaker beat.

Description of arrhythmias

Escape-capture bigeminy Bradley and Marriott[3] in 1958 named the electrocardiographic pattern produced by an escape beat followed by a normally conducted beat "escape-capture sequence." When the sequence repeats itself it is called "escape-capture bigeminy" In their original case the pattern was produced by a 2 1 sinoatrial block. Subsequently Schamroth and Dubb[4] described cases of escape-capture bigeminy initiated by 2 1 sinoatrial block, 3 1 A V block, and reversed reciprocal rhythm They pointed out that escape-capture bigeminy occurs when there is a marked discrepancy between the escape interval and the effective intersinus interval The effective intersinus interval is defined as the interval between sinus impulses at the level of the lower escaping pacemaker

Escape-capture bigeminy due to pacemaking on demand describes the situation in which a pacemaker induced escape beat is followed by a conducted supraventricular beat Castellanos and associates[1] described the only case of demand pacemaker induced escape-capture bigeminy in a patient with a 3 2 A V block and the Wenckebach phenomenon labeling it "iatrogenic escape-capture bigeminy" Complete capture of the ventricles by the artificial pacemaker in their patient occurred during alternate beats when conduction of the sinoatrial impulse was blocked

Escape-capture bigeminy occurred in 6 patients in the present series but none of them had the Wenckebach phenomenon. Four were in regular sinus rhythm and in 2 of them there was a first degree heart

Table I. Summary of cases

Patient no.	Sex age	Case history	Usual ECG	ECG during attack (if recorded)	Arrhythmia during pacing
1	F 75	HCVD palpitations and dizziness for 1 year with 3 episodes syncope	Sinus bradycardia rate 48 Atrial fibrillation rate 150	None	Escape-capture bigeminy Concertina effect
2	F 63	HASCVD dizziness for 2 years, with 2 episodes syncope during past year	Sinus bradycardia rate 46 Atrial fibrillation rate 110	None	Escape-capture bigeminy
3	M, 72	ASHD old diaphragmatic wall myo. inf. 5 episodes syncope during past year	RSR first degree HB	None	Escape-capture bigeminy
4	M 77	No known heart disease 6 episodes syncope in 3 years	RSR first degree HB LBBB	None	Escape-capture bigeminy
5	F 82	No known heart disease hypothyroidism 5 weeks intermittent dizziness	Sinus bradycardia rate 50 RBBB	RSR 2:1 HB rate 33	Escape-capture bigeminy Pacemaker ventriculophasic sinus arrhythmia
6	F 78	ASHD old anterior wall myo. inf. Intermittent dizziness for 1 year	Sinus bradycardia rate 40-50	Same rate 30	Trigeminy
7	M 87	No known heart disease Intermittent dizziness for 2 days post cystotomy	Pre-op RSR first degree HB LBBB Post-op Atrial flutter varying block rate 60	Atrial flutter varying block rate 50	Trigeminy
8	M 71	No known heart disease 1 syncopal attack 1 month ago, with subsequent dizzy spells	RSR abnormal left axis deviation RBBB	None	Escape-capture bigeminy Concertina effect
9	M 47	RHD with aortic insufficiency complete heart block following Starr Edwards prosthetic replacement of aortic valve	Pre-op RSR abnormal left axis deviation LVH Post-op Day 1 RBBB Day 5 complete HB Day 6 first degree HB RBBB→	None	Post-extrasystolic pacemaker escape

Abbreviations: HCVD, hypertensive cardiovascular disease; HASCVD, hypertensive arteriosclerotic heart disease; ASHD, arteriosclerotic heart disease; RHD, rheumatic heart disease; myo. inf., myocardial infarction; RSR, regular sinus rhythm; HB, heart block; LBBB, left bundle branch block; RBBB, right bundle branch block; LVH, left ventricular hypertrophy.

block. One had sinus arrhythmia and Patient No. 6 had sinus bradycardia. Two variations of the escape-capture sequence were present. The pacemaker escape beat was manifest as either a pacemaker induced QRS complex (Fig. 1) or a fusion or pseudofusion beat (Fig. 2).

The ECG in Fig. 1 *A* was recorded 4 months after pacemaker placement in a patient whose preoperative ECG showed regular sinus rhythm, first degree heart block, and a right bundle branch block pattern (Patient No. 3). The ECG shows slight sinus arrhythmia with a rate of 62 beats per minute and an R R interval of about .96 sec., which is the same as the escape interval of the demand pacemaker. The tracing shows a run of bigeminal rhythm. The third and fifth complexes are pacemaker escape beats. Because of the sinus arrhythmia, the natural R R interval exceeds the pacemaker escape interval of .96 sec. after the second and fourth beats, accounting for pacemaker escape beats 3 and 5. Supraventricular capture occurs during the fourth beat instead of an anticipated pacemaker escape beat because the pacemaker escape interval is greater after a pacemaker beat than after a supraventricular beat (1.00 sec. and .96 sec., respectively). Varying pacemaker escape intervals occur because the preceding QRS complexes are of different configurations, i.e., different slopes of the R wave. Since the demand pacemaker functions by sensing a two millivolt deflection of preceding R wave and timing its escape interval from that moment, a different R wave slope may delay the onset of the pacemaker escape interval. The pacemaker will then fire after a longer interval.

The ECG in Fig. 1 *B* was obtained eleven days after pacemaker implantation in a patient whose preoperative ECG showed sinus bradycardia at a rate of 50 beats per minute and a right bundle branch block pattern (Patient No. 5). The patient's cardiac rate now ranges from 62 beats per minute with an R R interval of .96 sec. to a rate of 83 beats per minute with an R R interval of .72 sec. The pacemaker is

Table II. Arrhythmias during demand pacing

Arrhythmia	No. of patients
Escape-capture bigeminy	6
Pacemaker ventriculophasic sinus arrhythmia	1
Trigeminy	2
Post-extrasystolic pacemaker escape	2
Concertina effect	2

set to escape after an interval of .86 sec., or at a rate of 70 beats per minute. Because of marked sinus arrhythmia, the natural R R interval exceeds the .86 sec. pacemaker escape interval, which allows the pacemaker to escape during beats 2, 4, and 6. Supraventricular capture, instead of pacemaker escape, occurs .86 sec. after the sixth beat because of a greater pacemaker escape interval following a pacemaker beat.

The ECG in Fig. 2 *A* was also obtained from Patient No. 3 two days after pacemaker implantation. *The tracing shows a slight sinus arrhythmia, with a rate of 65 to 67 beats per minute and an R R interval of .90 to .92 sec. Fusion beats 2, 4, 6, and 8 are formed because of nearly identical natural R R intervals and pacemaker escape intervals of .92 sec.*

The ECG in Fig. 2 *B* was recorded nine days after pacemaker implantation in a patient who had had sinus bradycardia at a rate of 42 beats per minute preoperatively (Patient No. 2). *The tracing shows slight sinus arrhythmia with an average natural rate of 67 beats per minute, i.e., an R R interval of .90 sec., which approximates the pacemaker rate. Because at times the rates are identical, the ventricles are nearly simultaneously activated by the supraventricular impulse and pacemaker, and fusion beats result (complexes 3 and 6).* The pacemaker fires, but does not activate the ventricles because of preceding supraventricular depolarization during beats 4 and 8, forming pseudofusion beats.* The pacemaker does not fire .90 sec. after fusion beats 2 and 6 because of a greater escape interval due to a different slope of these beats.

*Pseudofusion beat is pacemaker artifact superimposed on supraventricular conducted beat, superficially resembling fusion beat.

ESCAPE CAPTURE BIGEMINY

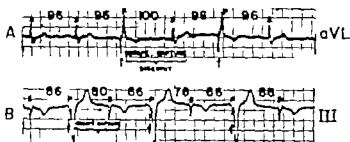


Fig. 1. Escape-capture bigeminy consisting of a sequence of a pacemaker escape beat (*P*) followed by a supraventricular capture beat (*S*). *A*, In a patient with regular sinus rhythm. *B*, In a patient with sinus arrhythmia.

ESCAPE CAPTURE BIGEMINY WITH FUSION AND PSEUDOFUSION

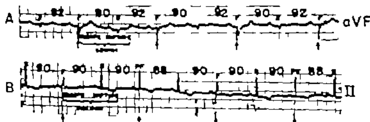


Fig. 2. *A*, Escape-capture bigeminy consisting of a sequence of a pacemaker fusion beat (*F*) followed by a supraventricular capture beat (*S*). In a patient with regular sinus rhythm. *B*, Escape-capture bigeminy consisting of a sequence of a pseudofusion beat (*PF*) followed by a supraventricular capture beat, in a patient with regular sinus rhythm.

Pacemaker ventriculophasic sinus arrhythmia. Ventriculophasic sinus arrhythmia describes the situation in which the P-P interval, embracing a QRS complex, is shorter than the following P-P interval. The pattern has been described in the presence of complete heart block, 2:1 atrial tachycardia, or ventricular premature systoles. Postulated mechanisms of ventriculophasic sinus arrhythmia include a baroreceptor type reflex or mechanical traction of the contracting ventricle upon the right atrium. One patient showed this phenomenon.

In Fig. 1 *B* the P-P interval, including the pacemaker beat of .72 to .82 sec., is shorter than the other P-P intervals of .96 sec. This may represent an example of pacemaker-induced ventriculophasic sinus arrhythmia in which the P wave following a pacemaker beat occurs earlier than anticipated. However, since longer strips are not available, marked sinus arrhythmia is an alternate interpretation.

Trigeminy. Trigeminal rhythm classically is described as a normal beat followed by two extrasystoles. In recent years, the arrhythmia in which two normal beats are followed by an extrasystole is also called a trigeminy. We have used the term trigeminy to describe a repetitive sequence of 3 beats composed of either a supraventricular beat followed by a fusion beat and a pacemaker beat, or a supraventricular beat followed by 2 pacemaker beats (Fig. 3). Two patients showed this phenomena.

The ECG in Fig. 3 *A* was recorded eight days after pacemaker implantation in a patient who had had atrial flutter and advanced heart block with an average ventricular rate of 60 beats per minute preoperatively (Patient No. 7). The ECG shows atrial flutter with variable block and a natural ventricular rate of approximately 62 beats per minute, i.e., an R-R interval of .96 sec. which approximates the pacemaker escape interval. This trigeminal rhythm consists of a supraventricular con

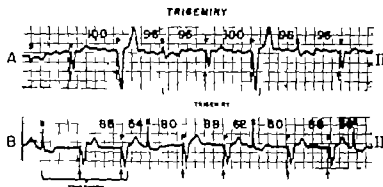


Fig 3 A Trigeminy consisting of sequence of a supraventricular beat (S) followed by a pacemaker fusion beat (F) followed by pacemaker beat (P) in a patient with atrial flutter with varying block. B Trigeminy consisting of sequence of supraventricular beat (S) followed by two pacemaker beats (P) in a patient with regular sinus rhythm

ducted beat (fourth and seventh complexes) followed by a fusion beat (second fifth and eighth complexes) and a pacemaker beat (third and sixth complexes) The escape interval after a supraventricular beat is 96 sec which approximates the natural R R interval and accounts for fusion beats 5 and The escape interval after a fusion beat is 1 sec (because of the different slope of the fusion beat) which exceeds the natural R R interval accounting for pacemaker beats 3 and 6 The escape interval after a pacemaker beat is greater than 96 sec accounting for supraventricular capture during beats 4 and 7

The ECG in Fig 3 B was obtained one day after a pacemaker was implanted in a patient whose preoperative ECG had shown sinus bradycardia at a rate of 40 to 50 beats per minute (Patient No 6) The natural rate is 52 beats per minute with an R R interval of 1 14 sec The pacemaker is set to escape after approximately 80 sec. at a rate of 75 beats per minute Trigeminal rhythm in this patient consists of a repetitive sequence of a conducted supraventricular beat (complexes 1 4 and 7) followed by two pacemaker beats (complexes 2 3 5 6 8 and 9) The first of the two pacemaker beats occurs because the pacemaker escape interval after a supraventricular beat is 80 sec which is less than the natural R R interval The second pacemaker escape occurs because the supraventricular impulse falls during the refractory period of the first pacemaker beat and cannot be conducted to the ventricles. The escape interval after a pacemaker beat is 88 sec instead of 80 sec. because of a different slope of the preceding pacemaker beat Supraventricular capture during beats 4 7 and 10 occurs because the 88 sec. escape interval is exceeded

Post-extrasystolic pacemaker escape The partial or full compensatory pause that usually follows a supraventricular or ventricular premature beat may not occur in the presence of a demand pacemaker if the pacemaker escape interval is less than the compensatory pause interval Post extrasystolic pacemaker escape occurred in 2 patients 1 with supraventricular and ventricular premature beats, and 1 patient with only ventricular premature beats.

The ECG in Fig 4 A was obtained 3½ months after pacemaker implantation in Patient No 3 The supraventricular rhythm is regular sinus rhythm alternating with coronary sinus rhythm. The pacemaker is set to escape after an interval of 1 06 sec. or at a rate of 56 beats per minute Atrial or nodal premature beats with aberrant conduction (complexes 2 and 5) are followed by pacemaker escape beats (complexes 3 and 6) presumably because the pacemaker escape interval of 1 06 sec is less than the interval of a beat occurring after a compensatory pause

The ECG in Fig 4 B was taken in the same patient 4½ months after pacemaker implantation. The basic rhythm is regular sinus rhythm with a cardiac rate of approximately 71 beats per minute and an

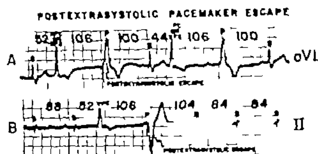


Fig. 4. A, Atrial or nodal premature beats (APC or NPC) followed by pacemaker escape beat (P) in patient with regular sinus rhythm alternating with coronary sinus rhythm. B, Ventricular premature beat (VPC) followed by pacemaker escape beat (P) in patient with regular sinus rhythm.

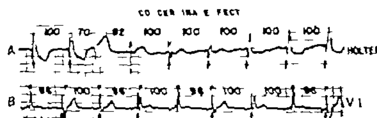


Fig. 5. Concertina effect consisting of a series of fusion beats (F) of varying configuration between supraventricular (S) and pacemaker (P) focus. A, In patient with sinus bradycardia. B, In patient with regular sinus rhythm.

R-R interval of .84 sec. The pacemaker is still set to escape after an interval of 1.06 sec., or at a rate of 56 beats per minute. The third beat is a premature ventricular systole followed by a pacemaker escape beat.

Concertina effect. The Wolff-Parkinson-White electrocardiographic pattern may manifest itself as a gradual increase and decrease in the height and width of the QRS complex, presumably due to varying amounts of ventricular musculature undergoing premature excitation. This phenomenon is called the concertina effect. A similar pattern with progressive changes in the configuration of the QRS complex may be demonstrated in a series of demand pacemaker fusion beats. Two patients manifested the concertina effect: the first sporadically, the second repeatedly.

The ECG in Fig. 5, *A* is an Avionics Holter* tracing taken ten days after pacemaker implantation in a patient whose preoperative ECG showed sinus bradycardia at a rate of 48 beats per minute (Patient No. 1). The patient is in regular sinus rhythm with a cardiac rate of 60 beats per minute and an R-R interval of about 1 sec. The pacemaker is set to pace at the same rate. The first two complexes are pacemaker beats, the third and fourth complexes are conducted supraventricular beats, the fifth and sixth complexes are fusion beats of different configuration, and the last three complexes are pacemaker beats. The transition from supraventricular beats to fusion beats to pacemaker beats resembles the concertina effect. When the pacemaker escape interval of approximately 1 sec. equals the patient's natural R-R interval, fusion beats 4 and 5 result. The fusion beats vary in configuration probably because of small changes in pacemaker escape intervals after a supraventricular and fusion beat of varying configuration, in addition to slight changes in the patient's natural R-R interval.

The ECG in Fig. 5, *B* was recorded one day after pacemaker insertion in a patient with regular sinus rhythm, an abnormal left axis deviation, and a right bundle branch block preoperatively (Patient No.

*Ten hour ECG recording on magnetic tape, using Model 330 Electrocardiocorder manufactured by Avionics Research Products Corporation.

ventricular rate is 60 to 62 beats per minute with a varying R R interval of 96 to 1 00 sec The pacemaker is set to escape after an interval of approximately 96 sec. or at a rate of 62 beats per minute. The first fifth and eighth beats are conducted supra ventricular complexes the second and ninth complexes are pacemaker beats, and the remaining complexes are fusion beats The pacemaker escape interval after a upraventricular beat is 96 sec. which is less than the natural R R interval ac ounting for pacemaker beats 2 and 9 The escape interval after a pacemaker or fusion beat varies from 96 to 1 00 sec. which approximates the patient s own R R interval accounting for a series of fusion beats.

Discussion

Several authors have described new iatrogenic disorders of rhythm secondary to electrical pacing f the heart comparing them with naturally occurring extents[1 · 4] Burchell and associates reported during as nchronou fixed r te cardiac pacemak ng 2 1 p c aker block interference hissociation pher omena with aberrant ven t icular c du ti n when the pacemaker timulus fell n a narrow interval at the end of the absolute refractory period and sorhythm i dissociation with accrochage and synchronization Linenthal and Zoll[10] llu trated fusion beats similar to those seen in the Wolff l arkinson White syn drome during fixed rate cardiac pacing and such fusion beats were subsequently demonstrated by Adelman and Lopez in a patient with an atriosynchronized pace maker

Castellanos and associates illustrated new arrhythmias following implantation of atriosynchronized pacemakers. These included pacemaker escapes (from sinus control) dissociation between atria and pacemaker (A P dissociation) with ven tricular captures (by the sinus node) the firing of the iatrogenic pacemaker by spontaneous A V nodal beats and ectopic ventricular contractions (N I and V I rhythms, respectively) and escape-capture bigeminy To date the only arrhythmia described during asynchronous demand pacemaking is iatrogenic escape-capture bigeminy

Summary

Five unusual arrhythmias which appeared in 9 patients with permanent transvenous Chardack-Greatbatch demand pacemakers are described Escape-capture bigeminy trigeminy and the concertina effect were due to slight changes in the supraventricular and pacemaker rates. Changes in pacemaker rate were dependent upon variation in configuration of the preceding QRS complex. Post-extrasystolic pacemaker escape occurred in the presence of an ectopic supraventricular or ventricular impulse. Pacemaker ventriculophasic sinus arrhythmia occurred because of the possible influence of a pacemaker-induced ventricular complex on the rhythmicity of the sinus node. All patients were asymptomatic when the arrhythmias were recorded

The cardiac pacemakers were implanted by Drs. Robert Litwak and How rd Gadboys.

REFERENCES

1 Castellanos, A J Budkin, A and Lemberg, L. Iatrogenic escape-capture bigeminy Brit Heart J 29:264 1967
2. Lemberg, L., Castellanos, A., J and Berkovits, E. E. Pacemaking on demand in AV block, J A. M A. 191 12 1965.
3 Bradley S. M nd Marriott, H J I Escape capture bigeminy Report of case of A V dissociation initiated by 2 1 S-A block and resulting bigeminal rhythm Am. J Cardiol 1:640, 1958.
4 Schamroth, L. nd Dubb, A.: Escape-capture bigeminy Mechanisms in S-A block, A V block, and reversed reciprocal rhythm, Brit. Heart J 27:667 1965
5. Rosenbaum M B nd Lepeschkin, F : The effect of ventricular systole on auricular rhythm i auriculoventricular block, Circulation 11:240, 1955.
6. Scherf D Problem of nomenclature in cardiac arrhythmias Am. J Cardiol 19:327 1967
7 Oehnell R. F Pre-excitation cardiac abnormality Acta med scandinav (Suppl) 152 1 1944.
8. Burchell, H. B Analogy of electronic pacemaker nd ventricular parasystole with observations on refractory period, supernormal phase and synchronization, Circulation 27:878, 1963
9 Burchell, H B Connolly D C., and Ellis F H Jr Indications for and results of implanting cardiac pacemakers Am. J Med 37 764 1964
10. Linenthal A. J nd Zoll P M Ventricular fusion beat and myocardial conduction time in man their significance for anomalous AV excitation, Tr A. Am Physicians 76:272, 1963

11. Adelman, A. G., and Lopez, J. F.: Arrhythmia associated with the synchronous pacemaker, Am Heart J 74:632, 1967
12. Castellanos, A. J., and Lemberg, L.: Disorders of rhythm appearing after implantation of synchronized pacemakers, Brit. Heart J 26:747, 1964.
13. Holmes, L. B., Spach, M. S., Canent, R. V., J., Brown, I. W., Jr., and Whalen, R. E.: Unusual observations during pacemaker therapy for complete heart block, Am. J. Cardiol 13:828, 1964
14. Soloff, L. A.: Iatrogenic parasystole and interpolated premature ventricular beats, Am. Heart J 63:563, 1962.

Experimental and laboratory reports

The relationship between the inotropic and dromotropic effects of digitalis: The modulation of these effects by autonomic influences

Iaul C Ogden M D
Irthur Sel-er M D
Keith E. Cohn M D
San F ancisco C lif

It is generall s umed that the inotropic and atriove tri ular blocking (dromotropic) effects f l gitalis change in a proportionate f shion —that with progressi e accumulation f digitalis glycosides, variation in ne f these parameters is mirrored by a imilar hange in the other Although Gold and co-workers[1,2] did not specifically study this point during their las ic studies three decades ago they did state that Dec l ne in ventricular rate is a good index f therapeutic action and runs fairly p rallel with improvement in failure

This study was undertaken in order to investigate the relationship between the inotropic and dromotropic effects of digi tali The importance of changing autonomic influences on these digitalis effects is also clarified in th s report

Methods

Twenty-six mongrel logs weighing 15 to 25 kilograms wer anesthetized with intra venou pent l arbit l sodium 30 n g per kilogra l rior t beg nning a l finitive tu ly nall a l lit l amount were added if needed to maintain general anesthesia The chest was opened through a bilateral thoracotomy incision and the heart suspended in a pericardial sling Respiration was maintained through a cuffed endotracheal tube attached to an automatic fixed volume Palmer respirator pump employing a 50 per cent oxygen mixture. Periodic sighing was manually performed Arterial pH pO_2 and pCO_2 values were regularly monitored utilizing a Beckman blood-gas analyzer and necessary respiratory or metabolic adjustment were made before an experimental run in order to maintain chemical neutrality Employing a roller pump the right ventricle was bypassed by withdrawing blood from the right atrium with a single catheter or from both venae cavae with two catheters and returning it directly into the pulmonary artery Efficiency of the bypass was confirmed by a definite soft consistency of the right ventricular wall on palpatati n an l l y me nitoring a low and constant right atri l or vena caval pressure Arterial a l venou pres ures were l t u ed through a Statha i P23 Db tran

From Depart e of Car iology Presbyterian Hospital, Pa Med al enter S ncisco, al . Supported i n t by ar HL 05693 al HL 7 07 and special fellowsh C F3 HE 36 . from the N onal I es of Health United States Public Health Service
Rec ed R. l A . 5 196

gauge and measured on an Electronics for Medicine multichannel recorder.

Myocardial contractile force was measured with a Honeywell myocardial force transducer sutured directly onto the right ventricular wall. Atrial stimulation was performed with a Medical Electronics Laboratory, Colmar, Penna. Stimulator through clips attached directly to the atrial wall. The resting heart rate was determined and the pacer then adjusted to a slightly faster rate so that constant heart rate could be maintained during all recording of contractile force. Atrial fibrillation was produced by pacing at rapid rates (15 to 50 per second); this induced an irregularly irregular ventricular rhythm. When the stimulator is turned off, the rhythm spontaneously reverts back to sinus. Throughout the remainder of this paper the term "ventricular response" will be used to signify the ventricular rate during atrial fibrillation and is therefore considered a measure of atrioventricular (A-V) conduction. While A-V nodal conduction is a function of both the A-V functional refractory period and the extent of concealed conduction, ventricular response was chosen here as the index of A-V conductivity principally because it is the variable most often affected clinically.

Before beginning right ventricular bypass, heparin sodium was given in a dose of 3 mg. per kilogram intravenously. Digitalization was then accomplished with bolus injections of intravenous acetylstrophanthidin,* giving incremental amounts averaging 1 to 25 mg. every three minutes. The terms "digitalis" or "digitalis glycosides" are hereafter used synonymously with acetylstrophanthidin (AS).

At three to four minute intervals the following were determined: (1) nonpaced rhythm, (2) myocardial contractile force measured at a fixed paced rate throughout the study, and (3) ventricular response. The appearance of digitalis toxicity was signified by the onset of cardiac arrhythmias, usually multiple ventricular ectopic beats, idionodal or idioventricular rhythms, or A-V dissociation.

The effect of AS on contractility and A-V conduction was studied under a variety of conditions. The 13 control animals were subjected to no other intervention. In 9 animals atropine sulfate given intravenously in doses of 0.8 to 1.2 mg. was used to produce parasympathetic blockade. This dose effectively abolished the action of acetylcholine (1 to 5 mg. given intravenously) on heart rate or ventricular response. In four dogs beta-adrenergic blockade was produced with MJ 1999 (Sotalol),† a drug believed to have little quinidine-like property. The completeness of the blockade was judged by the failure to increase contractile force or sinus rate following provocation with 4 μg bolus injections of isoproterenol. In another eight animals the effect of AS was assessed under varying levels of beta-adrenergic stimulation induced by infusion of isoproterenol (1 to 8 μg per minute). These studies were performed as follows: Contractile force and ventricular response were recorded under control conditions and during either one or two dose levels of isoproterenol infusion. The dose of isoproterenol was varied in each study so as to produce either maximal or varied levels of submaximal augmentation of contractile force. Contractility in the control and beta-stimulated states were always measured during equivalent paced rates. AS was then administered again in doses of 1 to 25 mg. approximately every three minutes and as the degree of digitalization progressed the contractile force and ventricular response were determined under control and beta-stimulated conditions. Performed in this manner, each animal served as its own control. The t test was used to estimate the significance of the differences observed.

Results

Full digitalization—levels attained just prior to toxicity—produced a 56 ± 10 per cent mean increase in myocardial contractile force and a 33 ± 3.2 per cent reduction of ventricular response (Table I). The relationship between the percentage change in contractility and the percentage

*Kindly supplied by G. — Chen, M.D., Eli Lilly and Company, Indianapolis, Ind.

†Kindly supplied by H. P. Mack, M.D., Mead Johnson Research Center, Evansville, Ind.

Table I. Response to acetylstrophanthidin under various autonomic conditions

Drug	Mean ventricular response (beats/min) (S.E.M.)	Mean per cent change vent. scale response A	B	Mean per cent change contractile force C	D
Base line	243 ± 9				
AS	166 ± 17		−32.7 ± 3.2		+56.1 ± 10.3
MJ 1999	147 ± 8	−39.5 ± 2.2		−0.2 ± 0.9	
MJ 1999 and AS	148 ± 4†		+0.6 ± 1.0†		+46.7 ± 1.8
Isoproterenol	268 ± 17	+8.2 ± 1.8		+110 ± 21.1	
Isoproterenol and AS	196 ± 20†		−28.2 ± 3.5		+22.0 ± 4.6
Atropine	239 ± 12	−1.6 ± 1.1		N‡	
Atropine and AS	164 ± 20		−30.6 ± 5.7		+75.1 ± 20

Legend: A and C: Mean percentage change of ventricular response or contractile force from base line, brought about by MJ 1999, isoproterenol, or atropine.
B and D: Mean percentage change induced by acetylstrophanthidin (AS) (measured from the level achieved after beta-adrenergic stimulation or blockade or parasympathetic blockade).
*Indicates significant change ($p < 0.01$) by paired t test.
†Indicates significant difference in response to AS compared with the controls.
‡N: Not recorded.

change in A-V conduction, however, varied from animal to animal and from moment to moment in a given animal during the course of digitalization (Fig. 1). In four dogs these two parameters changed in a proportionate manner as digitalization progressed (Fig. 1, A). In the other nine animals these two responses did not vary proportionately; at times the contractile force increased without concomitant change in A-V conduction, and in other instances the A-V blockade became more marked as the contractile force maintained a given level (Fig. 1, B and C).

Parasympathetic blockade. Atropine-induced parasympathetic blockade did not alter the variability seen in the relationship between increased contractility and increased A-V blockade. Atropine administration resulted in little or no increase in ventricular response in the nondigitalized animal, probably reflecting the high sympathetic tone of these open-chested animals. Definite slowing of A-V conduction in fully atropinized animals was seen sometimes after even a single small dose of AS (Fig. 1, D). Full digitalization in these dogs resulted in a 75 ± 20 per cent increase in contractility and a 31 ± 5.7 per cent slowing of ventricular response, values which are not significantly different from controls (Table I).

Beta-adrenergic blockade. Beta-adrenergic blockade did not alter the resting myocardial contractile force, nor did it influence the positive inotropic effect of AS, as evidenced by a mean increase in contractility of 47 ± 1.8 per cent with full digitalization (Table I). MJ 1999 elicited a profound slowing of A-V conduction in the undigitalized dogs, the mean ventricular rate declining from 243 to 147 beats per minute (39.5 per cent decrease). Digitalization in these beta-blocked animals then produced little or no further slowing of ventricular rate, the mean rate at full digitalization was 148 beats per minute (Fig. 2, A).

Beta-adrenergic stimulation. In the undigitalized animals, varying amounts of isoproterenol infusion caused an augmentation in contractile force of 31 to 183 per cent (110 ± 21 per cent mean increase) and a significant increase of 8.2 ± 1.8 per cent in ventricular response ($p < .01$, Fig. 2, Table I). Administration of digitalis induced comparable reduction in ventricular response in control and beta-stimulated animals, the control rate declining 33.1 ± 5 per cent and the beta-stimulated rate declining 28.2 ± 3.5 per cent. However, the slowest attained ventricular response at full digitalization remained significantly higher ($p < 0.01$) with exogenous beta

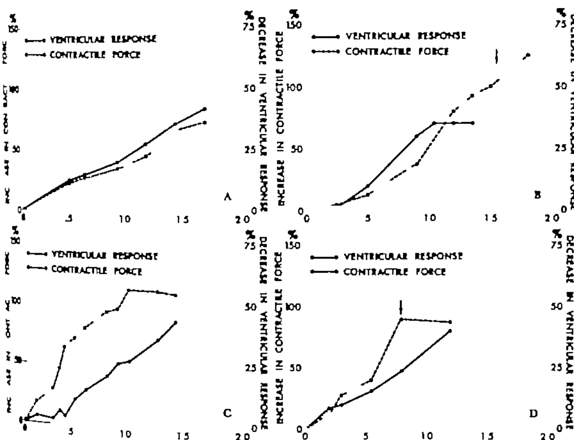


Fig. 1 The percentage increase in contractile force and percentage decrease in ventricular response are plotted against acetylstrophanthidin dose (in milligrams) from four experiments. In *A* contractile force and ventricular response change proportionately. *B* The two parameters are essentially proportionate but during the latter phase of digitalization ventricular response plateaus while contractile force continues to rise. *C* Initially contractility increases while ventricular response changes very little; later contractile force levels off and ventricular response continues to decline. *D* During parasympathetic blockade, the slowing of ventricular response begins early concomitantly with the onset of augmented contractile force. Arrow indicates onset of toxicity.

stimulation than without (mean 196 versus 166 Fig. 2, *A*).

The maximal developed contractile force induced by AS alone was invariably less than that attained with moderate to high doses of isoproterenol. In 13 animals AS increased contractile force an average of 86 per cent. Isoproterenol then increased contractile force by an additional 126 per cent. These percentage changes are calculated using the base line predigitalis value as the denominator. When isoproterenol and AS were administered concomitantly the peak contractile force reached was mainly dependent on the dose of isoproterenol employed (Figs. 2 *B* and 3). At high infusion rates of isoproterenol (4-8 μg per minute or 4-8 μg boluses) the contractile force produced by isoproterenol alone appeared to be maximal and was not further influenced by AS. At lower infusion rates of isoproterenol which produced submaximal increments in contractile force, AS did contribute to a further augmentation in contractility. Figs. 2 *B* and 3 demonstrate that at relatively low isoproterenol infusion rates the AS and isoproterenol appear to be additive with regard to contractile force. At slightly higher rates of isoproterenol infusion digitalis augmented contractile force only slightly since the contractility was already quite high. Overall the increment in total contractile force evoked by AS in the beta stimulated animal averaged only 22 ± 4.6 per cent and was significantly lower than the increase in the control situation (64.1 ± 11 per cent) ($p < .01$).

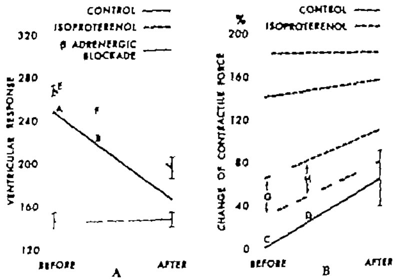


Fig 2 Ventricular t d ring trial fibrillation (A) and percentage change in contractile force (B) are show before d at peak dig t lization the control state during beta-adrenergic blockade, and at varying levels of beta adrenergic tim l tion (B show four representativ examples from eight studies). The brackets in A show the S E of the paired differences and the bracket in B depicts the S.E. of the mean control alues.

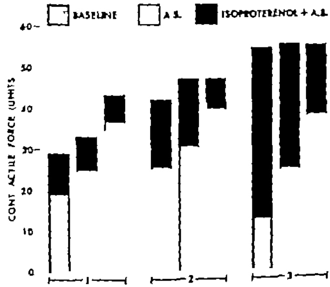


Fig 3 Bar graph f om three experiments showing the contractile force (in mm. paper) under the basal condition and after sopr terenol nd or AS. 1 1 AS and isoproterenol (low doses) are additive. 2, The contractile elling is ttained b combined AS and isoproterenol (second bar), so that increasing subtoxic doses of AS fail to ugment the total contractile force further 3, High doses of isoproterenol produce maximal contractile force and addition of AS does ot alter this level

In most of the animals, doses of AS above those noted to produce toxicity were administered and these induced a further increase in contractile force amounting to a 29 per cent average increment above the level attained at full subtoxic digitalization. This effect was seen both during the continued presence of toxic arrhythmias and after the arrhythmias had been abolished by ventricular pacing. Contractility was never measured in such an instance unless the heart rate was comparable to control and unless beats which were or post-ectopic could be measured

Isoproterenol successfully abolished several cases of digitalis-toxic arrhythmia: one instance of atrial tachycardia, two of nodal tachycardia, one A-V dissociation and four or five of multiple ventricular extrasystoles. In many instances of *early* digitalis toxicity isoproterenol produced a sinus tachycardia and abolished the arrhythmia transiently. In approximately one third of these instances, the normal rhythm *remained* even after the chronotropic and inotropic effects of isoproterenol had disappeared. In more advanced forms of digitalis toxicity produced with larger doses of AS, isoproterenol was generally unsuccessful at abolishing the arrhythmia and often failed to augment contractile force at all.

Discussion

It is apparent from these studies that the positive inotropic and the negative dromotropic effects of digitalis need not be parallel or proportionate to each other. Contractility may increase without constant change in A-V conduction or vice versa. Since two major factors known to influence contractile force, heart rate and fiber stretch, were controlled in our experiments, it seems reasonable to assume that such discrepancies may be caused by variation in autonomic stimuli. This is supported by observations after parasympathetic and beta-adrenergic stimulation and blockade.

Neither the inotropic nor dromotropic effects of AS were significantly altered by atropine-induced parasympathetic blockade. It is interesting to note that after administration of atropine there was no delay in the onset of A-V blockade produced by AS, a definite ventricular slowing being noted after even the smallest initial doses of AS had been administered. These observations conflict with the widely accepted belief[4] that low doses of digitalis control ventricular rate in atrial fibrillation by a vagal mechanism and only high doses directly influence A-V nodal conduction. It appears from this study that an extravagal, probably direct, action of digitalis plays a significant role in the initial slowing of A-V conduction.

The beta-adrenergic system seems to modify the inotropic and dromotropic effects of AS to a significant extent. It is shown that beta-adrenergic blockade with MJ 1999 does not alter the inotropic effect of digitalis, but produces a slowing of A-V conduction to such an extent that AS is incapable of producing a further negative dromotropic effect. The failure of beta-adrenergic blockade to alter the inotropic effect of digitalis confirms earlier studies[6-] which showed that in the catecholamine-depleted, sympathectomized, or beta-blocked preparation digitalis maintains its usual inotropic action.

These observations have lead us to question the belief held by several workers, that digitalis glycosides possess antiadrenergic activity.[10] This theory evolved after previous studies showed that in sympathectomized or reserpinized animals the A-V functional refractory period is markedly prolonged and that the further influence of digitalis on the A-V FRP was then diminished. It appears to us that several different factors act upon A-V conduction simultaneously, sympathetic and parasympathetic stimuli and drug effects being of major import. There appears to be, in addition, a *maximum* degree of A-V blockade short of complete heart block, which can be attained. Catecholamine depletion or beta-adrenergic blockade seems to bring about this maximal degree of A-V blockade and once this point is reached digitalis is incapable of further diminishing ventricular response apart from producing complete A-V block. Conversely beta-adrenergic stimulation speeds A-V conduction in the presence or absence of digitalis to an equal extent. In our opinion then, digitalis is not actually antiadrenergic. Rather it is merely one of several factors influencing A-V conduction and simply is ineffective in the beta-blocked state because maximal prolongation of A-V conduction has already been attained.

Beta-adrenergic stimulation with isoproterenol was shown to influence the inotropic as well as the A-V blocking effects of AS. Since isoproterenol alone enhances A-V conduction,[11] speeding up ventricular rate in atrial fibrillation, digitalis exerts its ventricular slowing effect in beta-stimulated animals by starting at a higher ventricular rate after full digitalization

the slowest attained heart rate is also more rapid than in the non-beta-stimulated animals. In the presence of beta adrenergic stimulation the inotropic effect of digitalis is variable, the influence of digitalis on further increasing contractility depending predominantly on the dose of isoproterenol employed. If only modest doses of isoproterenol are infused, the inotropic effects of the two drugs are additive, producing a greater contractile force when used together than either one alone would have. However, when large doses of isoproterenol are infused, a maximal effect (a ceiling) is achieved and addition of AS becomes ineffective. If moderately large yet submaximal doses of isoproterenol are infused, digitalis will evoke a much less pronounced further increase in contractility. It is evident that the increment in tension produced by AS depends upon the degree to which contractility has already been changed by the beta-stimulating agents.

The beta adrenergic synergism and antagonism with digitalis may well be responsible for the lack of parallel action of AS upon contractility and A-V conduction. This is explained in Fig. 2. Administration of AS would normally move ventricular response down the line from A to B and contractile force along the line from C to D. During digitalization, should the animal become hyperadrenergic from endogenous stimulation, the ventricular response might then move to point F and contractility to point H. Thus endogenous catecholamine stimulation would accentuate the inotropic effect while at the same time depressing or blocking the reduction in ventricular rate. Conversely, if the degree of endogenous or exogenous adrenergic stimulation were initially high and then diminished during the course of digitalization, the slowing of ventricular rate during atrial fibrillation would be especially pronounced (moving from E to B) while contractility would vary insignificantly (moving from G to D).

Some other aspects of the interactions between digitalis and isoproterenol deserve comment. We have confirmed earlier studies[22,23] which have shown that digitalis in "supratoxic" amounts is capable of further augmentating myocardial contractile force. In our study isoproterenol was shown to be capable of raising contractile force even beyond the levels attained by the supratoxic doses of digitalis. Thus, beta adrenergic stimulating agents have a far greater inotropic potency than digitalis glycosides do. There is a point of advanced digitalis toxicity, however, when the contractile force becomes depressed and when isoproterenol no longer retains the capacity of augmenting contractile force, suggesting that the digitalis-induced decrease in cellular maximum resting potential, action potential amplitude, and phase 0 dV/dt[1, 12] were no longer reversible by isoproterenol.

Isoproterenol successfully abolished some of the rapid and slow arrhythmias produced by digitalis. In some animals, this effect lasted for the brief durations that isoproterenol had exerted its inotropic action, but in others the rhythm remained normal even after the effects of isoproterenol had worn off. The mechanisms of the transient effect could be related to the capability of isoproterenol to increase the slope of phase 4 depolarization and sinoatrial node automaticity so that the resulting sinus tachycardia effectively competes with the digitalis-produced ectopic foci. Also, isoproterenol enhances A-V conduction[1] and thereby may abolish digitalis-toxic A-V block. The more prolonged antiarrhythmic effect of isoproterenol may be related to a reversal by isoproterenol,[24] of the decrease in maximal diastolic membrane potential[23] and of the non-uniformity of ventricular cell recovery[11]—both produced by digitalis toxicity. With severe degrees of digitalis toxicity, these electrophysiological abnormalities were probably no longer reversible by isoproterenol, since isoproterenol then failed to augment contractility, increase sinus rate, or abolish the arrhythmia. *It is noteworthy* that in only three experiments was a digitalis-induced arrhythmia worsened by isoproterenol.

Summary

The relationship between the inotropic and A-V blocking effects of acetylstrophanthidin (AS) was investigated *in* 76 dogs. Myocardial contractile force (CF) was measured with a strain gauge on the

bypassed right ventricle and A V conduction was assessed by determining ventricular rate (VR) during induced atrial fibrillation. No consistent relationship between these two variables was found moreover digitalis effect could be modified by controlling the autonomic environment Beta adrenergic blockade (with MJ 1999) did not impair the inotropic effect of AS but did elicit such marked slowing of ventricular response (243 to 147 beats per minute) that AS was then incapable of producing further A V delay Beta-stimulation (with isoproterenol) increased CF and thus limited the additional inotropic effect of AS (22 per cent increase in CF versus 64 per cent in the nonstimulated state) and resulted in a higher VR for any given level of digitalization (average 30 beats per minute higher) Isoproterenol had a greater inotropic potency than AS and successfully abolished several digitalis-tic arrhythmias.

We conclude that the inotropic and A V blocking actions of digitalis do not vary proportionately since digitalis action is modulated by changing autonomic stimuli. Neither the degree of digitalization nor the effects of digitalis on contractility can, therefore, be estimated simply by observing digitalis influence on A V conduction.

REFERENCES

1 Gold, H K ft, N T Otto, H. and Fox, T Physiological adaptions in cardiac slowing by digitalis and their bearing on problems of digitalization in patients with auricular fibrillation, J Pharmacol. & Exper Therap. 67:224 1939
2 Gold, H et al. Clinical studies on digitoxin (digitaline Nativelle) with further observations on its use in single averag f ll dose method of digitalization, J Pharm col. & Exper Therap. 82 187 1944
3 Sasaki, P and Lam, B K. B Blockade of epinephrine- and ouabain-induced cardiac arrhythmias in the dog heart lung preparation, J Pharmacol. & Exper Therap. 152:235 1966.
4 Moe, G. K., and Farah, A. E. Digitalis nd llied cardiac glycosides, Goodman L nd Gilman, A., editors The pharmacological basis of therapeutics ed. 3 New York, 1965 The Macmillan Company p 674
5. Modell, W The pharmacologic basis of the use of digit lis in congestive failure Physiol. & Pharmacol. for Physicians 1 1 1966.
6. Vinosky J nd Ervin, R The effect of ouabain on cardiac tomaticity reserpine-pretreated dogs Am. Heart J 62:687 1961
7 Boy jy L P and Nash C R I fluence of reserpine on arrhythmias notropic effects and myocardial potassium balance induced by dig talis materials J Pharmacol & Exper Therap. 148 193 1965
8. Levy J V and Richards, V Inotropic effects of ouabain on rabbit left tria in presence of beta-adrenergic blocking drugs, Proc Soc Exper & Biol Med. 119:278 1965
9 Mendez, C Aceves, J and Mendez, R The anti-adrenergic action of digitalis on the refractory period of the AV transmission tem J Pharmacol. & Exper Therap 131 199 1961
10 Morrow D H Gaffney T E and Braunwald E. Studies on digitalis VIII Effect of utonomic Innerv tion and of myocardial catecholamine tores upon the cardiac action of ouabain, J Pharmacol & Exper Therap 140:236 1963
11 Linhart, J W Braunwald, E and Ross, J J Determina t of the duration of the refractory period of the trioventricular nodal system man J Cli I vest. 44:883 1965
12. Williams, J F Klocke F J and Braunwald E Studies on digitalis XIII A comparison of the effects of potassium on the inotropic and arrhythmia-producing actions of ouaba n, J Clin. Invest. 45:346 1966
13 Scherlag B. J Helfant, R. H nd Damato, A. N Dissociation of the ionic inotropic and electro-physiological effects of digitalis with diphenylhydantoin or cardiac pacing Circulation (Suppl. II) 26:230, 1961
14 Singer D H Lazzara, R. nd Hoffman, B F I terrelationships between automaticity and conduction in Purki je fibers, Circulation Res. 21:537 1967
15 Hoffman, B. F nd Singer D H Effects of digitalis on electrical activity of cardiac fibers, Prog Cardiovas. Dis. 7:226 1964
16 Han, J nd Moe, G K. Nonuniform recovery of excitability in ventricular muscle Circulation Res 14:44 1964.

Phentolamine Use in digitalis induced arrhythmias

Canine experiments

Stephen Ettinger D V M
Lawrence Gould M D
J Andrew Carmichael M A Vet M B M R C V S
Robert J Tashjian V B V M D
New York and Bronx N Y

The beneficial effect of phentolamine (Regitine) in drug induced cardiac arrhythmia has been documented in experimental work in dogs. In our recent studies on this agent in man we also observed that its administration resulted not only in an improvement in left ventricular function but also in a disappearance of any coexisting ventricular premature contractions (VPC's). To further investigate this antiarrhythmic effect of phentolamine studies on digitalis-induced arrhythmias in 10 normal dogs were done

Methods and materials

Ten normal mongrel dogs were tranquilized with acetylpromazine (Acepromazine) 1 mg per 20 lb of body weight 30 minutes prior to the experiment No other drugs were administered Ouabain was administered intravenously on a milligram per pound basis, estimating the total dose at 0.02 mg per pound The drug was given at 20 minute intervals 50 per cent of the calculated dose was administered followed by 25 per cent every 20 minutes until toxic levels were attained Although each dog had episodes of vomiting nervousness, and occasionally diarrhea intoxication was firmly established on the basis of a persistent electrocardiographic abnormality

Each dog was monitored continuously on a cardioscope short strips of the electrocardiogram (ECG) were recorded at 5 minute intervals, or more frequently when intoxication occurred Toxic states were determined by the persistence of an electrocardiographic abnormality for over [illegible] minutes.

When toxicity had been established the dogs were given a constant intravenous infusion of phentolamine (15 mg in 200 cc solution of 5 per cent dextrose and water at the rate of 0.3 mg per minute (60 drops per minute) Lead II of the ECG was monitored continuously and recorded frequently during the infusion

Three normal dogs were tranquilized and given ouabain in the same manner as the experimental group. When electrocardiographic abnormalities persisted for over ? minutes, no other pharmacologic agents were administered These dogs served as controls to determine the natural course and duration of ouabain toxicity If the arrhythmia appeared to endanger the dog

Received for publication Aug 23 1968.
*From the Section of Cardiology The Animal Medical Center New York, N Y
**From the Medical Service of the Veterans Administration Hospital, Bronx, N Y

ile an intermittent intravenous infusion of lidocaine was begun in order to diminish the ectopic beats temporarily

Results

Each dog required surprisingly large doses of ouabain to reach toxic levels when the glycoside was administered in divided doses at 20 minute intervals The average total dose required was 0 62 mg or 0 024 mg per pound of body weight for healthy mongrel dogs ranging in weight from 16 to 38 lb. (Table 1)

Sinus bradycardia and first degree heart block (*Case* 2) After a 5 minute infusion of the drug, there was an increase in the heart rate, from 50 to 60 beats per minute and a shortening of the P R interval, from 0 20 to 0 14 sec. (Fig 1)

Complete heart block (*Case* 5) After a 24 minute infusion of phentolamine, the ECG of one dog indicated that a sinus rhythm had been reestablished although first de gree heart block persisted

Ventricular rhythms

VENTRICULAR TACHYCARDIA (CASES 3 7 8 9 AND 10) After one dog (Case 3) devel oped ventricular tachycardia phentolamine infusion for 15 minutes caused no change in the ECG In Case 7 phentolamine infusion for 4 minutes after the appearance of ven tricular tachycardia resulted in reversion to a sinus rhythm Following restoration of a sinus rhythm the infusion was stopped and after a delay of 2 minutes atrial tachy cardia developed this latter arrhythmia re sponded to phentolamine infusion with rapid reversion to a slower sinus rhythm

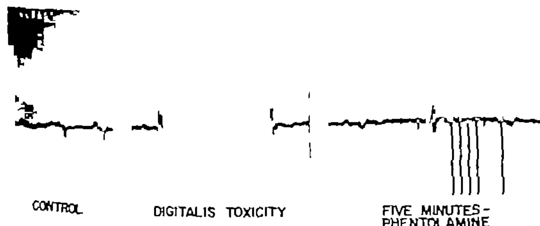


Fig. 1. Case 2 Normal control ECG followed by sinus bradycardia produced by intra venous administration of ouabain. Five minutes after phentolamine (Regitine) infusion as initiated the third tracing of sinus rhythm was recorded. (Paper speed 50 mm. per second, time lines 0 1 sec)

Table 1. Intravenous digitalizing doses of ouabain

Case No	Weight (lb)	Total dose (mg)	Electrocardiographic abnormality
1	35	0 625	Frequent multifocal VPC's
2	24	0 625	First degree heart block sinus bradycardia
3	33	0 750	Ventricular tachycardia
4	24	0 500	Frequent multifocal VPC'
5	16	0 525	Complete heart block
6	24	0 625	Bigeminal rhythm
7	20	0 500	Ventricular tachycardia
8	23	0 680	Ventricular tachycardia
9	18	0 800	Bidirectional entricular tachycardia
10	25	0 600	Ventricular tachycardia

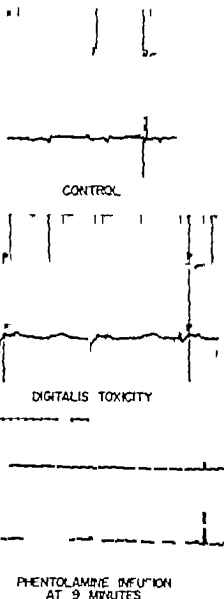


Fig 2 Case 8 Control ECG followed by entric lar rhythm induced by tr enous administ tion of ouabain. Nine minutes after phentolamine infusion was infuated the rhythm returned t a normal sinus pacemaker (P per peed 50 mm per second, time lines 0.1 sec. Lead II ECG)

After 9 minutes of intravenous phentolamine another dog (Case 8) reverted from a ventricular tachycardia to a normal sinus rhythm (Fig 2) A bidirectional ventricular tachycardia occurred in Cas 9 and sinus rhythm was reestablished 5 minutes after phentolamine infusion wa initiated (Fig 3) Five minutes after giving phentolamine infusion to a dog (Case 10) with digitalis-induced ventricular tachycardia, the ECG showed a normal sinus rhythm

VENTRICULAR PREMATURE CONTRACTIONS (CASES 1 4 AND 6) One dog (Case 1) developed multifocal VPC's following intravenou adminı tration of ouabain and phentolamine infusion relieved the abnormal beats after 9 minutes Seven minutes after the infusion was discontinued, unifocal VPC's developed In Case 4 phentolamine was given after the development of multifocal VPC's, and a sinus rhythm was reestablished after 17 minutes. In Case 6, bigeminal rhythm resulted from the glycoside infu ion after 2 minutes of phentolamine infusion a sinus rhythm returned

Each dog was monitored for several hours after the experiment and maintained a normal cardiac rhythm

In summary 9 dogs reverted to a normal sinus rhythm after phentolamine was infused In one case of ventricular tachycardia phentolamine was ineffective

In 3 control dogs who were given ouabain until toxic levels were attained but were not given phentolamine the arrhythmias (ventricular tachycardia) lasted for 120, 100 and 55 minutes respectivel or an average of 92 minutes. Two of the 3 dogs developed ventricul r tachycardia of such severity (lasting for 1 0 n 1 100 minutes) that intermittent intravenous infusion of lidocaine was indi ted

Discussion

Previous studies i this laboratory have indicated that at the dosage rate of 0.3 mg. per minute of phentolamine there was no reduction in systemic blood pressure and no untoward effects were observed These findings were confirmed in the present study when this critical dose of phentolamine was administered to 10 dogs with acutely induced digitalis intoxication. Further th cardiac rhythm was converted to normal with phentolamine in 9 out of 10 cases.

In 3 control dogs ouabain-induced ventricular tachycardia persisted for an average of 92 minutes (120 100 and 55 minutes, respectively) Intermittent lidocaine therapy diminished the persi tent ectopia temporarily Since this latter therapy did not abolish the abnormal rhythm the duration of intoxication could be determined

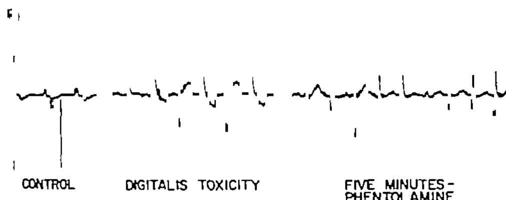


Fig. 3 Case 9. Control tracing followed by bidirectional ventricular tachycardia produced during digitalis intoxication. The final tracing shows the ECG 5 minutes after phentolamine infusion was begun. This tracing shows the transitional stage from the bidirectional tachycardia to sinus rhythm. (Paper speed 50 mm. per second, time lines 0 1 sec.)

electrocardiographically. In our clinical experience in dogs with spontaneous heart failure, ouabain-induced toxicity often persists for several hours.

In his experimental work on dogs, Leimdorfer[1] demonstrated in 1952 that the administration of phentolamine prevented atropine sulfate and epinephrine-induced arrhythmias and converted methacholine-induced atrial flutter fibrillation, and atrioventricular nodal rhythm to normal sinus rhythm. He further showed that phentolamine administration prevented the appearance of pronounced bradycardia during electrical stimulation of the vagus nerve. He concluded that phentolamine had the property of reverting the abnormal heart rhythm to normal by inducing the normal sinoatrial pacemaking function. However, he did not elaborate on its mode of action.

Recently, Dairman and his associates[4] presented data suggesting the mechanism of action of phentolamine. They administered phentolamine (5 mg. per kilogram) to rats. At the height of alpha-receptor blockade, the conversion of a tracer dose of tyrosine-14C to norepinephrine in the heart, brain, and adrenal gland was increased threefold with no alteration in specific activity of tyrosine in blood and tissues. From these studies Dairman concluded that receptor blockade led to increased synthesis and release of norepinephrine in the three organs.

However, it is difficult to relate this new information to the abolition of digitalis-induced arrhythmias. Indeed, one would assume that increased production of catecholamines might stimulate the production of arrhythmias. Thus, the manner in which phentolamine blocks digitalis-induced cardiac arrhythmias remains unknown and is worthy of further investigation.

The present study has demonstrated that phentolamine, when administered at the dose of 0.3 mg. per minute, can reverse digitalis-induced arrhythmias in normal dogs with a high degree of success. It would now seem reasonable to administer the drug when digitalis intoxication occurs in human patients. Further, an investigation of phentolamine in arrhythmias not induced by digitalis might prove beneficial.

Summary

The antiarrhythmic effect of phentolamine was investigated in 10 normal dogs acutely digitalized with ouabain. Phentolamine was infused intravenously for an average of 10 minutes at 0.3 mg. per minute. Ventricular arrhythmias were abolished in 7 of 8 cases (there was complete heart block in 1 case) and the rate was increased in one case with sinus bradycardia. Administration of the drug produced no untoward side effects and did not produce hypotension.

These studies indicate that phentolamine may be of clinical value as an antiarrhythmic agent and warrants further study.

The authors wish to thank Mrs. Mary Brown for her assistance in the preparation of this paper.

REFERENCES

1. Leund fer A Abol tion of rdiac rhyth mia I Reg t Arch t ternat. pharmacodyn 96:239 1952
2. Lelmdr fer A Prevention nd abolition of cardiac arrhythmia by Reg tine Am J Phy iol. 1 1 742 1952
3. Gould I Zahir M nd Ett ger S Phento- lam ie nd rd a sc lar perf mance (Abstr) Am J C rd al 1 100 1968
4. Gould I Zahir M and Ettinger S Phento-lamine and cardiov sc lar perf ormance, Brit. Heart J In press.
5. Daleman, W Gordon, R Spector S, Sjoerdsma, A nd Udenfriend A Effect of lpha blockers on catecholamine release Fed Proc 27:240 1968

Measurement of collateral blood flow after myocardial infarction in the closed chest dog

Jacob I. Haft, M.D.
Anthony N. Damato, M.D.
Staten Island, N. Y.

The prognosis in clinical myocardial infarction may depend to a great extent on the amount of arterial blood that reaches the myocardium distal to occlusion.[1] In the experimental animal the measurement of the effective blood flow to an area that is rendered ischemic can be accomplished with the use of solutions of radioactive inert gases. Johansson and co-workers measured collateral flow by injecting krypton-85 into a coronary artery and then immediately occluding the artery distal to the injection. Sullivan and co-workers[3] determined effective flow in ischemic myocardium by intramyocardial injections of krypton distal to occlusion. The authors[4] have reported a technique in the open-chest animal utilizing a fine cannula placed in a coronary artery about which a ligature is tied occluding the vessel but not the cannula it contains. The falloff of radioactivity after krypton is delivered distal to the occlusion has been used to estimate effective collateral flow. Rees and Redding[5] have recently reported a similar technique using a fine nylon cannula inserted into a coronary artery distal to an occlusion with an injection of xenon into this area to estimate collateral flow.

All of these techniques have heretofore required thoracotomy. In order to more closely simulate clinical infarction, a method has been developed to estimate collateral flow in the experimental animal without the necessity of opening the chest. It is the purpose of this paper to describe this technique and present our early results with it.

Methods

Mongrel dogs lightly anesthetized with pentobarbital were used for the study. Standard ECG Lead II and peripheral blood pressure using a femoral artery catheter were monitored throughout the procedure. The coronary artery occlusion catheter is prepared as follows (Fig. 1). A "J" tip is fashioned at the end of a 15 inch length of standard No. 7 Teflon-coated cardiac catheter. A 20 to 25 inch length of No. 3 Teflon tubing (approximately 1 mm. in diameter) is placed in the lumen of the No. 7 catheter and advanced so that approximately 1 cm. protrudes from the "J" tip. A 2 to 3 mm. length of No. 7 Teflon tubing is placed over the cannula. The tip of the cannula is flared and bonded to the plug. The cannula in the catheter is pulled back so that the plug is flush with the tip of the catheter. Another catheter with the cannula in its lumen but

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
This work was supported in part by Bureau of Health Services, Division of Direct Health Services, United States Public Health Service Project Py 66-1, and National Institutes of Health Grant No. HE-[illegible].
Received for publication Aug. 27, 1968.

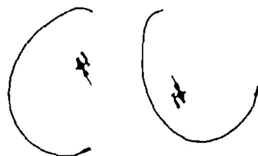


Fig. 1. The plug occlusion catheter. On the left the ... is seen extending through and beyond the ... tip of the catheter. The plug ... attached to the end of the ... On the right the ... has been pulled back through the catheter so that the plug ... flush ... the tip of the ... in the position for insertion of the plug.

without a bonded plug, is prepared and used for measurement of control flows.

The right carotid artery is isolated in the neck. Control flow in the area to be made ischemic is first determined by placing the catheter containing the cannula without the plug in the carotid artery and under fluoroscopic control the catheter is advanced into the left coronary ostium. The cannula is then advanced through the catheter approximately 4 to 6 cm. into the left anterior descending or circumflex artery to a point where occlusion will subsequently be made and the catheter is removed over the cannula. Control coronary flow is determined in duplicate by delivering ½ c.c. of a saturated solution of krypton-85 in saline into the artery and measuring the falloff curve of radioactivity with a 2 inch crystal detector counter which is positioned over the precordium. Blood flow is determined from the initial portion of the curve using the method of Ross and co-workers.

The control cannula without the plug is then removed. The catheter with the cannula in its lumen, to which is attached the plug at the distal tip, is then placed in the carotid artery and advanced under fluoroscopic control into the left coronary ostium. The plug and catheter are advanced as far as possible into the coronary artery (usually 4 to 6 cm.) and the plug is wedged. The catheter is then removed leaving the plug wedged in place. Effective flow distal to the occluding plug is then determined by injecting krypton-85 into the cannula and determining the falloff rate of radioactivity. Flows were determined immediately and 1½ hours after occlusion. In those dogs surviving 4 hours after the procedure, the cannula was flushed with heparin and temporarily sealed. The cannula was then coiled, placed under the strap muscles of the neck, and the cervical incision was closed. In 3 dogs that were not used for other studies, the incision was reopened 24 hours later and flow measurements were made.

Results

Fig. 2 shows the plug and cannula in position in the left circumflex coronary artery. The catheter used for positioning has been withdrawn into the ascending aorta.

Figs. 3 through 5 are radiographs of another dog in which the plug was placed in the left anterior descending coronary artery. Fig. 3 demonstrates the position of the plug, the cannula, and the catheter (which has been pulled back in the ascending aorta). For demonstration purposes, an angiogram of the vessels distal to occlusion was obtained by injecting Hypaque through the cannula and plug (Fig. 4). In the usual studies, radioactive krypton is delivered into this area and the blood flow arriving in this area (from collaterals) is measured by the resulting falloff curve of radioactivity. To demonstrate the blood flow proximal to the plug (Fig. 5) a second catheter was temporarily placed in the proximal portion of the left anterior descending artery. Hypaque injected through this catheter outlines the patent coronary artery and its branches and demonstrates the occlusion by the plug.

Following plug occlusion, all of the animals developed ST-T wave changes and within hours developed significant Q waves. Fig. 6 demonstrates the development of ECG changes typical of an inferior myocardial infarction in a closed-chest dog after plug occlusion of the circumflex artery.

Studies were performed on 16 dogs. The coronary blood flow prior to occlusion, immediately and 1½ hours after occlusion are presented in Table I. The mean control flow rate was 105 c.c. per minute per 100



Fig 2. The plug is in position in the left circumflex artery. Note the cannula attached t the plug nd that the catheter has been ithdra from the coronary artery over the cannula and is lying in the ascending aorta.



Fig 3. The plug in pos tion in the left anterior descend ng coronar artery. The catheter used for position ng has been thdra t he aorta



Fig 4. Hypaque has been injected through the cannula and plug into the area distal to the plug demonstrating the essels distal to the occluding plug

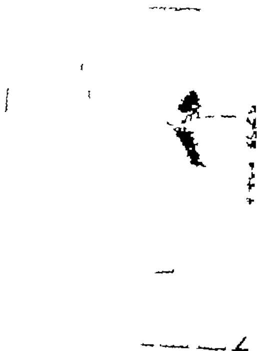


Fig 5. A second catheter was placed in the left anterior coronary artery proximal to the plug and Hypaque as injected to demonstrate vessels proximal to the plug. Not that no dye goes distal to the plug

Cm of ms cardium Following occlusion the mean blo l fl w dropped to 33 8 c c per minute per 100 C m and in 11 dogs was ?? ? after 1? hours The results are presented graphically in Fig 7 The mean percent g f ntr l fl w was 31 8 per cent immediately after occlusion and 30 2 per cent at 1? hours (Fig 8)

In order to verify the validity of the plug method of o clu ion the results were compared with those obtained using an open-

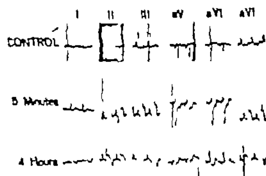


Fig 6 Electroc (g d g before d after plug lusion of the m ndex onary artery

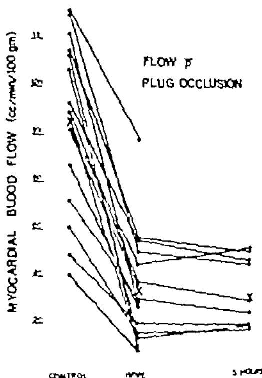


Fig 7 The change in flow after plug occlusion in 16 dogs The X signify the means

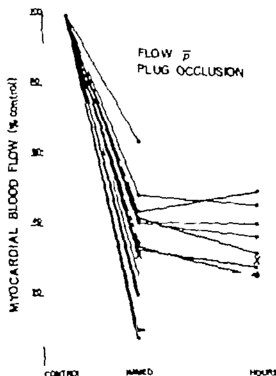


Fig 8 The changes in blood flow after plug occlusion with the result presented as per cent of control.

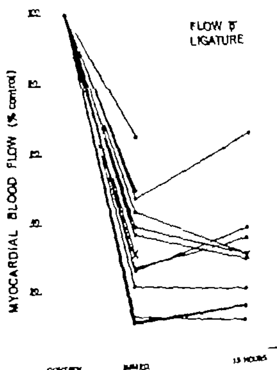


Fig 9 The changes in flow after ligature occlusion with the results presented as per cent of control

chest technique[4] in 14 dogs. In these animals, a fine cannula was placed in a branch of the left coronary artery. The chest was opened and coronary artery containing the cannula was isolated. After determining control flows a ligature was tied occluding the artery but not the cannula. The control flows and the effective flows distal to the tie after occlusion were similar to those found with plug occlusion in the intact animal (Table II). Mean drop in flow after tying was to 31.2 per cent of control

Table I. Results of plug occlusion

	Control (c.c./100 Gm./min.)	Immediately after occlusion (c.c./100 Gm./min.)	% Control	1½ hrs. after occlusion (c.c./100 Gm./min.)	% Control	24 hrs. after occlusion (c.c./100 Gm./min.)	% Control
	49	19.7	40.4	18.2	37.2		
	60.5	15.7	26	16.0	26.4		
	127	13.2	10.4	17.3	13.6		
	40.5	7.75	19.2	8.4	20.7		
	72	30.2	42	23.2	32		
	87	26.8	31.5				
	152	98	64.5			37	24.3
	135	56.5	41.4	49.7	40.7		
	113	55.3	48.7	52.2	46.1		
	133	9.4	7.6				
	109	37.4	34.2	28.2	25.9		
	150	50.5	33.7	43.8	28.3	15.9	10.6
	106	10.4	9.8	12.2	11.5		
	142	28.8	19.9				
	102	45	44	51.3	50	37	36.2
	102	36.2	35.2				
Mean	105.0	33.8	31.8	29.2	30.2		

Table II. Results of ligature occlusion

	Control (c.c./100 Gm./min.)	Immediately after occlusion (c.c./100 Gm./min.)	% Control	1½ hrs. after occlusion (c.c./100 Gm./min.)	% Control
	89.6	19.2	21.4	17.5	19.6
	84	41.3	49.5		
	95	10.8	11.4		
	64.5	17.2	27	24	37.2
	122	53	43.4	36	29.5
	76	29.7	39	22.4	29.5
	195	25.3	12.8	20.8	10.7
	80	37.8	45	52.4	65.5
	115	29.8	25.9	39.5	34.4
	96	10.5	10.9	13.8	14.4
	61.5	6.37	10.4	8.9	14.3
	75	49	65.3		
	115	36	31.2		
	152	55.5	36.4	43.2	28.4
Mean	106	30.1	31.2	27.8	28.4

in 14 dogs immediately after occlusion and to 28.4 per cent at $1\frac{1}{2}$ hours after occlusion (Fig. 9).

Of the 16 dogs subjected to plug occlusion 1 died within an hour of occlusion, 4 were put to death a few hours after the procedure, 2 were found dead the next day and 9 lived longer than 24 hours. All those living longer than 24 hours showed ventricular arrhythmias going in and out of ventricular tachycardia. Fig. 10 shows a typical arrhythmia. Coronary flows were recorded at 4 hours in 3 of these dogs and in all 3 cases were less than the values at $1\frac{1}{2}$ hour (Table I).

On postmortem examination those dogs killed a few hours after occlusion all showed areas of ischemia distal to the occlusion. Those animals examined after 24 hours showed infarction and inflammatory reaction in the area distal to the plug.

Discussion

The presence of collateral circulation in the coronary tree has been demonstrated using numerous techniques. Anatomical studies with injection dissection and radiographs of postmortem hearts have shown the presence of interarterial communications to a small extent in normal hearts but to a significantly greater extent in hearts that had major occlusion.[3,8] Glass and wax beads have been shown to pass from one major coronary artery to another confirming the presence of functional collateral vessels.[10-11]

The quantity of blood flow delivered to an ischemic area was first studied using backflow methods. In these preparations, a coronary artery was opened distal to an occluding ligature and the blood flow measured. The resulting flow was considered to be a measurement of the collateral circulation. Gregg and associates[14] reported backflow immediately after occlusion to be less than $1\frac{1}{2}$ c.c. per minute but to be up to 105 c.c. per minute months after ligation.

The availability of radioisotopes led to further studies of collateral circulation in the myocardium. MacLean and colleagues[17] showed that radioactive glass beads, 20 microns in diameter, entered areas of the myocardium distal to major artery occlusion in perfused dog hearts. They found the flow to be approximately 25 per cent of control values. Rubidium-86, an isotope that enters the myocardium in much the same manner as potassium, has been used to estimate collateral coronary flow. Chansky and Levy[3] found the flow to ischemic areas to be 33 to 75 per cent of control

24 Hours after Plug Occlusion

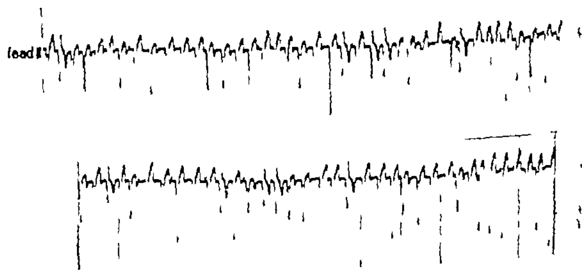


Fig. 10. A rhythm strip of a dog 24 hours after plug occlusion of the circumflex artery.

values. Their technique required that the animals be put to death soon after the administration of the isotope and a comparison made between the radioactivity in aliquots of heart muscle from ischemic and from normally perfused areas of the heart.

The physical properties of the radioactive inert gases, principally xenon and krypton, have made them useful in the study of coronary flow. These substances are (1) biologically inert, (2) diffuse readily across membranes and reach equilibrium very rapidly, and (3) are much more soluble in air than water. The radioactive material is almost completely removed from the blood stream during its initial circulation through the lungs. A bolus of saline containing krypton or xenon delivered into a coronary artery rapidly enters the myocardium, establishing an equilibrium between the radioactivity in the blood and that in the muscle cell. The charged-up muscle loses its radioactivity as isotope-free blood comes in contact with the muscle cells. The loss of radioactivity occurs as an exponential function with the rate constant depending on the blood flow. Although there are probably a number of compartments and hence a number of exponential falloff functions occurring simultaneously, the initial portion of the inscribed curve closely reflects the coronary blood flow. Since the gas almost completely escapes on passage of the blood through the lungs, there is no significant error introduced by recirculation of radioactive material. Both xenon and krypton have sufficient gamma emission to allow external measurement of the falloff curves and it is not necessary to use coronary sinus sampling.

The use of radioactive gases to measure blood flow to ischemic areas of the myocardium is dependent on the ability to deliver the tracer substance into the area that is not well perfused. If the gas solution is injected into the artery proximal to the occlusion, it will be delivered in great enough quantities only to those areas that are best perfused and the resulting curve will be essentially normal.[1] A number of techniques to circumvent this problem have been developed. Johansson and associates[1] injected krypton into a coronary artery and subsequently tied it off. They reported the flows distal to occlusion to be 5 to 30 mL per minute per 100 Gm. with control values of 55 to 150 ml. per minute per 100 Gm. Sullivan and co-workers[3] injected krypton directly into the heart muscle in ischemic areas. Harman and colleagues wedged a catheter into the coronary sinus and injected the isotopes retrograde into areas that had previously been made ischemic. From their illustrations, it appears that blood flow in ischemic areas decreased to about 75 per cent of control. More recently, Rees and Redding[4] implanted a nylon cannula in a coronary artery distal to a ligature occlusion. They found the flow immediately after occlusion to decrease to 25 per cent of values found in their control animals.

The drop of coronary blood flow to approximately 30 per cent of control which was found using the technique presented in this paper is in general agreement with the results reported by other investigators. The plug technique, however, has certain advantages over those previously reported. First, the entire procedure, which is performed in the closed-chest animal using only light anesthesia, more closely simulates the clinical situation. Second, the animal can serve as its own control. Third, the animal need not be killed, and repeat studies are possible over a period of hours and days. Chronic studies are not complicated by convalescence from a major surgical procedure and studies of the effects of drugs on collateral flow can be pursued without the hemodynamic changes that accompany surgical trauma. In addition, the electrocardiographic changes and cardiac arrhythmias which developed in these animals parallel closely the changes seen after clinical myocardial infarction. Finally, the technique is a relatively simple one and is not difficult for those skilled in coronary artery catheterization.

Summary

A technique is described whereby the blood flow distal to experimental occlusion of a coronary artery can be measured in the closed-chest dog. Coronary [illegible] fell to a mean of 31.8 per c[illegible] immediately following occl[illegible] showed electrocardiogra[illegible]

myocardial infa ti n This procedure may be of value n the stu ly of the effects of various inters nti ns on collateral circu lation foll wing xperim ntal infarction

REFERENCES

1 Blumg rt H L Anat my and functional import e f ter rona rterial anastomoses, Circ l 20 81 1959
2 Joha s B J k I nd Seema, T Collater l bl od fl w th m ocardium of dogs me sured b kr pt 85 Acta physiol. scandin. 6 61 1961
3 S llin J M l ke W J Elliott W C nd Gorl R C Cl f t am ocardial adio kr p der f eg nal my ardial bl f fl w Cir l on (Suppl II 32:204 1965
4 H ft J I l S H Scherl g B J nd D mats A A M ureme t of collateral blood fl w in xper me t l schemia Clin Res 14 4 3 196
5 Rees J R d Redding V J Anast mosic blood flow xperime l m c rd l infarc t on C rd s R 1 169 1967
6 Ross R S Ued K Lichtlen P I nd Rees J R M ur ment f m cardial blood flow m l d ma b select jection f d u t ne g t the coronary arteries Cir l t on Res 15:28-41 1964
7 Schlesinger M J A ject on pl dissec tion study f c r y artery oc lusions nd anastomoses Am H art J 15 528 1938
8 Blumgart H L Schles nger M J nd D vid, D Studies on the relat f the linic l m festation of ng na pect ris, coronary thrombosis nd m ocardial inf rction t the pathologic finding Am H art J 19 1 1940
9 Baroldi C M tero, O nd Scomazzoni, G The collater ls of the coronary arteries in normal and pathologic heart Circulation Res. 4:223 1956
10. Laurie W nd Woods, J D Anatomical of the coronary circulation, Lancet 2:812, 1958
11 Bellman S., and Frank, H A I tercoronary collateral in normal heart J Thoracic Surg 36:581 1958
12 Pepler W J nd Meyer B J Interarterial oronary na tomoses and ronary arterial pattern. A comparativ stud of South African nd European he rt Circulation 22:14 1960
13 Prinzmetal M Simkin, B Bergman, H. C, nd Kruger H E Studie of the coronary irculation. II The ll teral circulation of the normal human heart by coronary perfusion ith radioactiv erythrocytes and glass spheres, Am Heart J 33 420, 1947
14 Lutt, B I terarterial coronary anastomoses. Occurrence in normal hearts and in certain pathologic conditions, Circulation 20:816, 1959
15 Blonr C M nd Lichow A. A. Coronary collateral circulation Am J Cardiol 16:238, 1965
16. Gregg D F Thornton, J J and Mautz F R The magnitude adequacy and source of the collater l blood flow and pressure in chronically occluded coronary arteries, Am J Physiol. 127 161 1939
17 MacLean, L. D Hedenstrom, P H., and Kim, Y S Distribution of blood flow to the canine heart, Proc. Soc Exper Biol. 107 786, 1961
18. Chansk M nd Levy M H: Collateral circulation to myocardial region supplied by the nterior descending and right coronary arteries in th dog, Circulation Res 11:414, 1962
19 Harman, M A Markov A, Lehan, P A Oldel urtel, H A and Regan, T J Coronary blood flow measurement in the presence of arterial obstruction Circulation Res 19:632, 1966.

Effect of protokylol on the ventricular rate in dogs with experimental A-V heart block*

A. Scriabine, M.D. **
J. Rosal, M.D.
S. Bellet, M.D.
G. Morgan, Jr., B.S.
A. S. Weyn, M.D.
M. Nusbaum, M.D.
Philadelphia, Pa.

Among the sympathomimetic amines used in the treatment of patients with complete A-V heart block, isoproterenol is the drug of choice. By virtue of its positive chronotropic action on the atrial as well as ventricular pacemakers, isoproterenol can prevent or alleviate the Stokes-Adams syndrome. One of the drawbacks of isoproterenol is its short duration of action. In an attempt to improve isoproterenol, a sustained release form of the drug was developed. It is claimed to be effective in 50 to 65 per cent of patients with complete A-V heart block.[1,2] In the search for a longer acting beta-adrenergic stimulant our attention was drawn to protokylol[3,4] (see Fig. 1) which is presently used as a bronchodilator in the therapy of bronchial asthma. In this study we evaluated the effects of protokylol on the ventricular rate of dogs with experimental A-V heart block.

Methods

Nineteen mongrel dogs of either sex, 12 to 20 kilograms in body weight, were used for evaluation of the effects of protokylol on the heart rate of normal conscious animals. The dogs were trained to lie quietly on tables for periods up to 6 hours without restraint. Each treatment group (see Table I) consisted of 6 different dogs. Some of the animals were used two or three times, each time for a different treatment. At least three days were allowed between treatments. Protokylol was given by gastric lavage. The required dose was dissolved in 50 ml. water. In control experiments, the animals received the same amount of water only. For intravenous administration protokylol was dissolved in saline at 1 or 2 mg. per milliliter. Electrocardiograms, Lead II, were recorded with a Sanborn 500 one-channel recorder at 10 minutes prior to the drug administra-

From the Division of Cardiology, Philadelphia General Hospital and Department of Surgery, University of Pennsylvania Medical School, Philadelphia, Pa.
Supported by a grant from the Pennsylvania Heart Association to Dr. A. Scriabine.
Received for publication Aug. 28, 1968.
*Presented in part at the 1968 meeting of the Federation of American Societies for Experimental Biology, Atlantic City, N. J.
**Requests for reprints should be addressed to Dr. A. Scriabine, Present address: Merck Institute for Therapeutic Research, West Point, Pa. 19486.

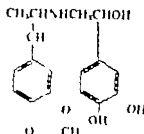


Fig. 1. Protokylol (JB-251, α-(α-methyl-3,4-methylenedioxy-phenethyl)amino-methyl-4-hydroxy-m-protocatechuyl alcohol. C ... line

tion and at 5, 15, 30, 60, 90, 120, 150, and 180 minutes after treatment.

Twenty-one mongrel dogs of both sexes and in the same body weight range as the first group of animals were anesthetized with sodium pentobarbital, a dosage of 35 mg. per kilogram given intravenously. They were then subjected to a surgical procedure consisting of thoracotomy, opening of the right atrium during temporary occlusion of large veins, and ligation of the bundle of His. The ligation was performed 5 to 10 mm. anterior to the coronary sinus along the axis of the A-V junctional area. The method was similar to that used by Starzl and Gaertner.[6] Starting with the fourth postoperative day, the animals were trained to lie quietly on tables and were subjected every three to four days to the same experimental procedure as the animals of the first group.

The statistical significance of the difference in the means of heart rate values was determined with the Student t test.

Results

In normal conscious dogs, protokylol increased heart rate at 0.25 mg. per kilogram and higher oral doses. The onset of action was rapid; at 0.25 and 1.0 mg. per kilogram the maximal positive chronotropic effect was observed 5 minutes after treatment. The duration of action of the orally administered protokylol given at 1 and 4 mg. per kilogram exceeded 3 hours. The maximal effect was obtained at 1 mg. per kilogram; there was no greater effect with an increase in the dose to 4 mg. per kilogram. By intravenous administration, protokylol produced greater cardiac acceleration than by oral administration of the same dose, 1 mg. per kilogram. This difference was apparent at 5 minutes after treatment; at 15 minutes there was no significant difference in the degree of cardiac acceleration caused by protokylol by two different routes. Water alone given orally had no effect on the heart rate (Table I). Protokylol produced no cardiac arrhythmias with any of the doses used.

The surgical procedure described in Methods was successful in producing a complete A-V block in 15 out of 21 dogs. The animals recovered within 24 hours with complete A-V heart blocks and stable ventricular rates of 30 to 50 beats per minute. Protokylol administered orally in dosages of 0.25, 1.0, and 4.0 mg. per

Table I. Effect of protokylol on the heart rate in normal conscious dogs

Group No.	Drug	Dose (mg./Kg.)	Route	Heart rate (beats/minute)†: 10 min. before drug	Min. after treatment: 5	15	30	60	90	120	150	180
1	Water only		Oral	80	85	81	80	81	77	81	88	80
2	Protokylol	0.25	Oral	79	158	151	143*	129*	112	112*	98	80
3	Protokylol	1.0	Oral	97	185*	178*	169*	173	158	146	146	135*
4	Protokylol	4.0	Oral	85	140*	157	165	163	152	150*	168	133*
5	Protokylol	1.0	Intravenous	86	203	185	173	185	168*	158	122	125*

*Significantly different from the control value before drug treatment, $p < 0.05$.
†Average values for 4 dogs in each group.

kilogram increased the ventricular rate (Fig 1 and Table II) The effect of protokylol at 4 mg per kilogram was not greater than at 1 mg per kilogram The maximal effect of the drug was observed at 5 to 30 minutes after treatment the duration of action exceeded 3 hours. In three additional experiments, not included in Table II protokylol given orally at 1 0 mg per kilogram increased ventricular rate for 3½ but not for 4 hours. The effect of protokylol administered intravenously at 1 mg per kilogram was not greater and of shorter duration than the same dose given orally Isoproterenol given orally at 1 mg per kilogram also increased the ventricular rate Its effect was, however considerably less pronounced than that of protokylol at the same dose An intravenous dose of isoproterenol given at 0 032 mg per kilogram caused only transient increase in the ventricular rate Administration of water had no effect on the ventricular rate

In dogs with the A V heart block the atrial rate was less regular than the ventricular rate The evaluation of the effects of drugs on the atrial rate was, therefore

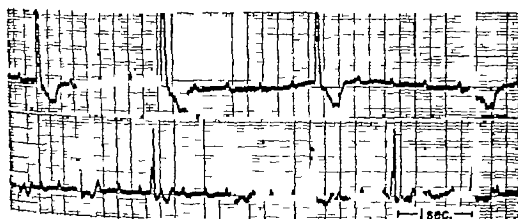


Fig 2. Electrocardiograms, Lead II from a female dog weighing 12 kilograms with experimental A V heart block, before and one hour after oral administration of protokylol, 4 mg per kilogram Note increase in the ventricular and atrial rates after treatment.

Table II *Effects of protokylol and isoproterenol on the ventricular rate in conscious dogs with experimental A V heart block*

Group No.	Drug	Dose (mg./Kg.)	Route	Ventricular rate beats/minute†									
				Before treatment	Min after treatment								
					5	15	30	60	90	120	150	180
1	Water only		Oral	46	46	47	45	43	44	45	46	44
2	Protokylol	0 15	Oral	41	45	48	51	47	48	45	46	42
3	Protokylol	1 0	Oral	44	64	63	60*	57	59	61	63	63
4	Protokylol	4 0	Oral	41	60*	61	60*	60*	64	63	63	63
5	Protokylol	1 0	Intravenous	36	64	57	55*	55	56	49*	45	40
6	Isoproterenol	1 0	Oral	41	53	53	52*	53	53*	50	45	47
7	Isoproterenol	0 032	Intravenous	35	50*	46	41	38	35			

*Significantly different from the control value before drug treatment, p < .05
†Average values for 4 dogs in each group

more difficult Increases in atrial rate were observed with protokylol as well as with isoproterenol The estimated average atrial rate for 6 dogs with A V heart block before protokylol was 172 beats per minute it was increased to 174 beats per minute at 5 minutes after protokylol 1 mg per kilogram administered orally Isoproterenol given orally at 1 mg per kilogram 5 minutes after treatment increased the average atrial rate in 6 dogs from 119 before to 153 beats per minute after treatment Protokylol in the doses used by us administered orally or intravenously produced no observable [illegible] effects in dogs.

Discussion

In dogs with experimental A V heart block protokylol effectively increased ventricular rate The average increase in the ventricular rate did not exceed 50 per cent of the control value whereas in normal dogs protokylol increased the sinus rate by over 100 per cent Since isoproterenol even by intravenous administration had no greater effect on the ventricular rate than protokylol it appears likely that under our experimental conditions, the ventricular rate cannot be increased by drugs to a greater extent But even if this is the maximum obtainable effect of protokylol under any conditions a 50 per cent increase in the ventricular rate of patients with a complete A V heart block may be sufficient to maintain cardiac output at reasonable levels and a greater effect may not be required

Of particular interest is the good oral activity and long duration of action of protokylol These properties may represent the main advantages of protokylol over isoproterenol. Since isoproterenol is known to be relatively poorly absorbed from the gastrointestinal tract it was not surprising that its positive chronotropic effect at 1 mg per kilogram given orally was not impressive But even by intravenous administration at a dose relatively high for isoproterenol it only transiently elevated the ventricular rate

Our data suggest that at sufficiently high oral or intravenous doses, the duration of action and the efficacy of protokylol may be sufficient for effective therapeutic management of A V heart block.

Summary

Protokylol is a beta-adrenergic stimulant which is presently used in the treatment of bronchial asthma. Given orally at 1 and 4 mg per kilogram protokylol increased heart rate in normal conscious dogs and ventricular rate in dogs with experimental A V heart block its duration of action exceeded 3 hours. Our data suggest the possible usefulness of protokylol in the therapy of A V heart block.

The authors are thankful to Dr R. C. Ursillo, Lakeside Laboratories, Milwaukee Wis., for supplying protokylol.

REFERENCES

1. Bellet, S. The drug treatment of complete A V heart block Ann. New York Acad Sc. 111:818 1964
2. Bluestone R., and Harris, A. Treatment of heart-block with long-acting isoprenaline. Lancet 1 1299 1965
3. Nissen, N I and Thomsen, A. C. Oral treatment of A V block and other bradycardias with sustained action isoprenaline Brit. Heart J. 27:926, 1965
4. Jacobi, H Koch K. and Schlewing, M Zur Pharmakologie des Protokylols, Arzneimittel-Forsch 13:51 1963
5. Leslie A and Simmons D H Evaluation of the bronchodilator C ytine (JB-251), Am. J. M. Sc. 233:3 1 1957
6. Starzl T E., and Gaertner R. A.: Chronic heart block in dogs A method for producing experimental heart failure Circulation 12:259 1955.

Effect of various diuretics upon experimental cardiac necrosis

Hans Selye M D Ph D D Sc
Montreal Quebec Canada

The fact that tissue electrolytes play an important role in determining the functional and structural integrity of the cardiovascular system has been amply substantiated. In particular numerous clinical and experimental data have demonstrated the existence of close connections between potassium and the actions of digitalis alkaloids, the marked effects of potassium deficiency or excess upon the myocardium and the dependence of hypertensive cardiovascular disease upon sodium These relationships are also strikingly illustrated by the experimental electrolyte-steroid-cardiopathies characterized by necroses (ESCN) which can be elicited by combined treatment with certain corticoids and sodium salts Even in themselves ineffective doses of electrolytes and steroids so prepare or condition the heart of the rat that massive infarctoid myocardial necroses regularly develop upon oral administration of lipids (e.g. corn oil) fatty acids, or exposure to stress (e.g. restraint, forced muscular exercise, cold) 3

No matter how produced the ESCN is readily inhibited by the oral administration of potassium salts. However the amount of potassium required is comparatively large and its effect is of short duration Some forms of the ESCN have also been prevented by the potassium-sparing aldosterone antagonists spironolactone and compound SC 11927 (3-oxo-9α fluoro-11β 1 β-dihydroxy 1 α pregn 4-ene 21-carboxylic acid) but with these the results obtained were less constant.

Amiloride a new nonsteroid potassium sparing agent is 180 times as active as spironolactone in its effect upon electrolyte metabolism This compound proved to be extremely potent in preventing even a very acute and severe form of the ESCN in which the cardiotoxicity of the pathogenic steroids and electrolytes is enhanced by the concurrent administration of lipids.

One of the greatest dangers in using saluretics in the treatment of cardiovascular disease is the loss of potassium consequently these drugs are commonly administered in combination with potassium sparing agents or dietary potassium supplements Therefore it seemed of interest to establish whether such saluretics would enhance the production of cardiac necroses of the ESCN type and if so whether their cardiotoxicity could be counteracted by concurrent treatment with amiloride.

Materials and methods

Holtzman farms (Madison Wisconsin) supplied 120 female rats with initial body weights of about 100 grams (range 90 to 110 grams) The rats were subdivided into

From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada.
This work was supported by the Ministère de la Santé, Québec, the Medical Research Council of Canada (Block Term Grant MT 1829) and the Geralex Research Foundation Ltd Toronto, Canada
Received for publication Sept. 13 1968

Table I. Effect of various diuretics upon experimental cardiac necrosis

Group	Treatment*	Cardiac necrosis (Scale 0-3)	Mortality (%)
1	None	1.1 ± 0.41	10
2	Amiloride	0	0
3	Hydrochlorothiazide	2.4 ± 0.24	90
4	Hydrochlorothiazide and amiloride	0.1 ± 0.1	20
5	Ethacrynic acid	1.5 ± 0.37	60
6	Ethacrynic acid and amiloride	0	0
7	None	1.0 ± 0.34	20
8	Amiloride	0	0
9	Hydrochlorothiazide	1.9 ± 0.34	100
10	Hydrochlorothiazide and amiloride	0	0
11	Ethacrynic acid	1.2 ± 0.58	20
12	Ethacrynic acid and amiloride	0	0

*In the first experiment (Groups [illegible]) amiloride, hydrochlorothiazide, and ethacrynic acid were given subcutaneously at the dose of 200 μg., in the second (Groups 7-12) per os at the dose of 500 μg. In addition to the treatments listed in this column, the animals of all groups received F-COL, Na_2HPO_4, and corn oil for the production of cardiac necrosis, as indicated in the text.

12 equal groups and treated as outlined in Table I. For the production of the ESCN fluorocortisol (750 μg. in 0.2 ml. water) was injected once daily subcutaneously and Na_2HPO_4 (1 mM in 2 ml. water) and corn oil (1 ml.) were administered twice daily by stomach tube. In the first experimental series (Groups 1-6) amiloride (N-amidino-3,5-diamino-6-chloropyrazinecarboxamide), ethacrynic acid [2,3-dichloro-4-(2-methylene-butyryl) phenoxy acetic acid] and hydrochlorothiazide (6-chloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4-benzothiadiazine) were given subcutaneously at the dose of 200 μg. in 0.2 ml. of water twice daily. In the second series (Groups 7-12) these compounds were given by stomach tube at the dose of 500 μg., the diuretics (whether administered alone or in combination) being added to the Na_2HPO_4 solution without increasing the volume of the solvent. Daily treatment with all drugs was initiated simultaneously on the first day of the experiment.

The severity of the cardiac necroses was estimated in terms of an arbitrary scale: 0, no lesion; 1, lesion just visible; 2, lesion pronounced; and 3, most severe lesions, as previously described. Table I lists the means of these readings (with their standard errors) including both the animals that died during the experiment and the remainder that were killed with chloroform after 6 days. The macroscopic findings were confirmed by histologic observation on paraffin-embedded sections stained with the PAS technique.

Results

As shown by Table I, the cardiac necroses and mortality were moderate in the controls of both series (Groups 1 and 7), and completely prevented by amiloride (Groups 2 and 8). Hydrochlorothiazide increased mortality to 90 per cent in the first and to 100 per cent in the second series (Groups 3 and 9). As judged by Table I, the cardiac damage was not as intensely augmented as the mortality rate, presumably because many of the animals died so early that there was not enough time for the structural cardiac damage to become evident. Ethacrynic acid proved to be somewhat less toxic than hydrochlorothiazide in aggravating the ESCN (Groups 5 and 11), but additional treatment with amiloride greatly diminished or completely abolished the cardiotoxicity of these diuretics both in the first and in the second series (Groups 4, 6, 10, and 12). This inhibition was evident macroscopically (Fig. 1) and could be confirmed histologically.

Discussion

Amiloride has already been used for other purposes in man and was found to be



Fig. 1. *Left:* Extensive infarction of right ventricle and apex in hydrochlorothiazide treated rat of Group 9. *Right:* Complete prevention of this necrosis by additional oral administration of amiloride.

a well tolerated and potent natriuretic and potassium-sparing agent; therefore its prophylactic action against cardiac necrosis appears to deserve further attention.

It remains to be shown whether the mechanism conducive to these experimental cardiac necroses is comparable to that responsible for cardiac infarction in man. The ESCN is a metabolic cardiopathy in which occlusion of the coronary arteries is not a primary phenomenon although occasionally thrombi develop secondarily within the damaged vessels of the necrotic regions. However numerous investigations suggest that the same is true of many cardiac infarcts in man since frequently occlusive thrombi are not demonstrable unless the patient survives long enough for clots to develop within the necrotic vascular territories (for literature see references 1 and). Although weight for weight extrapolations of drug actions from animal to man are always hazardous, it is also worth mentioning that on this basis, the dosages of hydrochlorothiazide and ethacrynic acid employed in our experiments roughly correspond to those recommended for the treatment of patients.

In any event the electrolyte-steroid treatment conducive to an ESCN creates a considerable predisposition for the development of cardiac necroses even without occlusive vascular changes. Hence the elucidation of the underlying mechanisms and the discovery of drugs that abolish this tendency to the formation of fatal myocardial damage may be of practical importance.

Summary

The production of a fatal "electrolyte steroid-cardiopathy characterized by necrosis (ESCN) is facilitated by subcutaneous or oral administration of hydrochlorothiazide or ethacrynic acid. Conversely amiloride prevents the development of an

LSCN not only when it is produced in the conventional manner but even when its severity and lethality are increased by additional administration of either hydrochlorothiazide or ethacrynic acid

The author wishes to thank the following companies for kindly supplying the compounds used in these experiments: Ciba Co., Ltd., Dorval, Quebec, Canada (hydrochlorothiazide); Merck Sharp & Dohme Research Laboratories, West Point, Pa. (Amiloride HCl and ethacrynic acid); and the Upjohn Company, Kalamazoo, Mich. (9α-fluorohydrocortisone acetate).

REFERENCES

1. Selye, H.: The chemical prevention of cardiac necroses, New York, 1958, The Ronald Press Co.
2. Selye, H.: The pluricausal cardiopathies, Springfield, Ill., 1961, Charles C Thomas, Publisher.
3. Selye, H.: Protection by a steroid-spirolactone against certain types of cardiac necroses, Proc. Soc. Exper. Biol. (New York) 104:212, 1960.
4. Selye, H., Gabbiani, G., and Padmanabhan, N.: Protection by antimineralocorticoid against an otherwise fatal dihydrotachysterol intoxication, Lancet 1350, 1960.
5. Cragoe, M. S., and Stedman, S. L.: N-amidino-3,5-diamino-6-chloropyrazinecarboxamide: an active diuretic in the carboxamide series, Nature 12 191, 1966.
6. Selye, H.: Prevention of cardiac necrosis by amiloride, J. A. M. A. 206 103, 1968.
7. Cannon, P. J., Freis, E. D., and Moghadam, A.: Effect of MK-870 in normal subjects and hypertensive patients, New England J. Med. 2?? 1215, 1966.
8. Berllnd, S., and Lundwall, O.: Serum electrolyte changes during long-term treatment with amiloride hydrochloride (MK-870), Acta med. scandina. 183:375, 1968.
9. Ramos, O. L., Ajzen, H., Andrade, L., Capella, J. J., Stella, S. R., and Kora, D.: Effect of MK870 administered alone and in association with ethacrynic acid on electrolyte and water balance on cirrhotic patients with ascites, Arch. bras. Endocrinol. 16 115, 1967.
10. Brunner, F. P.: Klinische Erfahrungen mit dem neuen kaliumsparenden Diureticum Amilorid (Moduretic, C hlectrol MK-870), Schweiz. med. Wschr. 97:1542, 1967.

Prevention of experimental atherosclerosis with pyridinolcarbamate

Chun-Chung Wu
Teh-Siu Huang
Cheng-Jen Hsu
T ipei, Taiwan

Atherosclerosis has become a major disease threat to the human population of Taiwan. The medical literature abounds with articles on the pathogenesis of atherosclerosis, and for almost five decades attention has been focused predominantly on lipid deposits in blood vessels.[1] The reason for this trend stems from the finding of abundant lipid deposit in atherosclerotic vessels, namely in atheromas, and from the successful production of atherosclerosis in rabbits who received cholesterol feedings.[2]

In 1957 Keys[3] reported that diet, through its fat content, played an important role in the development of coronary heart disease. Many attempts to alter the atherosclerotic lesion by correcting existing hypercholesterolemia have failed to provide definite evidence that a decrease in blood lipids will act to inhibit or reduce cholesterol accumulation in the arterial wall.

Edema of the inner layers of the arterial wall was first observed in 1856 by Virchow. Several decades later Bredt[4] and others described edema of the intimal ground substance and from this assumed that edema of subintimal tissue was an initial stage in the production of the atherosclerotic lesion.

In 1952 Pollak described an etiologic concept of atherosclerosis based on a study of intimal alterations following shock. He reached the conclusion that in all persons exposed to shock hydropic swelling of the initial endothelial cells was seen. He further stated that physicochemical disturbances of plasma colloids during shock initiated this hydropic swelling and that this initial change is then followed by increased permeability and seepage of plasma through the defective endothelium resulting in edema and hyaline mucoid change of the subintima.

After the breakdown of lipoproteins and resorption of most of the foreign material, lipids namely cholesterol remain in the subintima where they act as irritants and initiate the alterations which are generally known as atherosclerosis.

Recently Shimamoto and Sunaga[7] succeeded in producing an edematous arterial reaction by utilizing a number of experimental atherogenic procedures such as serial injections of epinephrine and force-feeding of rabbits with cholesterol. The reaction they produced consisted of an acute accumulation of serous substances in the subendothelial and medial layers, and adherence of platelets and leukocytes

From the Department of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan (Drs. ... Huang), and the Department of Pathology, Medical College of Taipei, Taipei, Taiwan (Dr. Hsu).
Received for publication Sept. 24, 1968.

to the endothelial surface. Shimamoto assumed that the initial stage of experimental atherosclerosis is characterized by an edematous arterial reaction. This phenomenon is closely similar to the type of arterial change seen in early human atherosclerosis as described above by Bredt. Shimamoto and his co-workers [11] have introduced pyridinolcarbamate which has an atherosclerosis-inhibiting effect in cholesterol fed rabbits and humans.

These findings suggest that atherosclerosis can be treated without correcting abnormal metabolism. This study was undertaken to analyze further the reported ability of pyridinolcarbamate to prevent atherosclerosis.

Methods and materials

Thirty male albino rabbits, with an average body weight of 2.0 kilograms, were used. The rabbits were divided into a control placebo group (13 rabbits) and a pyridinolcarbamate treated group (17 rabbits).

The former received a placebo capsule containing starch and the latter received 10 mg per kilogram of pyridinolcarbamate packed in gelatin capsules. The capsules were given daily at 9:00 A.M. All of the rabbits were kept on 1.5 Gm. of cholesterol mixed with a basic diet consisting of potato and rice. This feeding was given two hours after the capsules. The serum cholesterol level and total lipids were determined following the method of Bloor and Kunkel monthly. Each blood sample was drawn from the central ear artery prior to feeding. After 15 weeks all rabbits were put to death. The viscera were dissected out and immersed as quickly as possible in a 5 per cent glutaraldehyde solution. The aorta which was dissected out first was stained with Sudan IV after 24 hours of fixation. The Sudan IV positive areas, that is, the areas involved by atheroma or fatty streaks were beautifully demonstrated and the percentage involvement was calculated by mapping on transparent paper. The remaining viscera including heart, kidney, liver and sometimes the adrenal and brain were dissected out and fixed in a 10 per cent formalin solution. Representative sections of the viscera and aorta were made after careful inspection and stained with routine hematoxylin and eosin.

Results

In the treated group 5 animals died during the first 3 weeks. Examination revealed that 2 died of shock following violent insertion of the pyridinolcarbamate capsule, 1 died of suffocation when the capsule was accidently inserted in the trachea and the other 2 died following prolonged diarrhea. Among the control group only 1 animal died during the experiment and this was attributed to excessive diarrhea.

As shown in Fig. 1, the serum cholesterol level increased in stepwise fashion during the first 8 weeks to a level of 1,000 mg. per deciliter and then exhibited a slower increase in both groups. There was no statistically significant difference in serum cholesterol levels between control

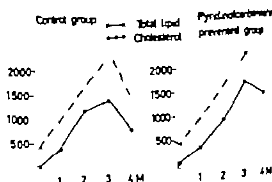


Fig. 1. Serum cholesterol and total lipid level of rabbits.

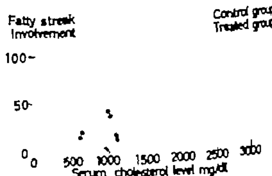


Fig. 2. Prevention against atherosclerosis by pyridinolcarbamate.

*Supplied by Banyu Pharmaceutical Co., Ltd. Japan.

and pyridinolcarbamate treated groups. The total lipids increased steadily to a level of 2 000 mg per deciliter at 12 weeks. Again, there was no statistically significant difference between the two groups.

Cardiovascular system

AORTA. The pathological findings in the aorta are summarized in Tables I and II and in Fig 2 The surface percentage of lipid deposition was definitely lower in the treated group, although there were a few exceptions in each group The average percentage involvements were 39 9 ± 18.8 per cent in the control group and 12 7 ± 12 1 per cent in the treated group The difference between the two groups was statistically significant at a level of P < 0 01 (Table I)

The relationship between the percentage of aortic fatty streak involvement and the mean serum cholesterol level during the last 8 weeks in the control and pyridinolcarbamate groups is shown in Fig 2. Pyridinolcarbamate prevented the formation of atherosclerotic lesions even when the serum cholesterol was markedly elevated

Microscopic study of aortic atheromas revealed that the atheromas of both groups were always well developed and usually located within the intima When the atheromas were large and thick, medial involvement was also noted When the thickest part of the atheroma was compared with the thickness of the remaining aortic wall as shown in Tables II and III it was found that the atheromas of the control group were thicker and medial

Table I. *Findings in the control and the pyridinolcarbamate-treated group*

	Control group (12 rabbits)	*Treated group (12 rabbits)*
Serum cholesterol level (mg/dL)		
Before	50	37
15th week	1 231	1 418
Fatty streak involvement (%)	37 9 ± 18 8	12 7 ± 12 1

Table II *Degeneration of heart tissue in control and pyridinolcarbamate-treated groups*

Control group					*Pyridinolcarbamate-treated group*				
Animal number	*Surface of aorta involved (%)*	*Thickness of atheroma/ thickness of aortic wall*	*Degree of coronary sclerosis*	*Degree of myocardial fibrosis*	*Animal number*	*Surface of aorta involved (%)*	*Thickness of atheroma/ thickness of aortic wall*	*Degree of coronary sclerosis*	*Degree of myocardial fibrosis*
[illegible]	26 6	3.2	Marked	Marked	575	8 6	1 1	Marked	None
[illegible]	48 3	1 1	Marked	Marked	576	9 6	1.2	Mild	None
[illegible]	74 2	4 1	None	None	577	7 8	2 1	Mild	None
[illegible]	64 4	1.1	Mild	Mild	578	0 1	0·1	Mild	None
[illegible]	22 1	2 1	Marked	Mild	579	4 0	1.2	—	—
[illegible]	18 0	1 1	Moderate	Mild	580	0	0.1	Moderate	Mild
[illegible]	13 1	3.2	Moderate	Mild	581	13 7	1 1	Mild	None
[illegible]	13 8	0 1	Moderate	Mild	582	0	0.1	Mild	None
[illegible]	49 4	1.1	Moderate	Mild	583	34 0	2.3	Mild	Mild
[illegible]	47 9	1 1	None	Moderate	584	13 2	1.1	Moderate	Moderate
[illegible]	33 8	1.1	Moderate	Marked*	596	29 0	2 1	Mild	Moderate
[illegible]	31 8	2.1	—	—	597	33 0	0.1	Moderate	Moderate
Average 37 9 ± 18 8					Average 12 7 ± 12 1				

*Myocardial fibrosis with recent myocardial infarction.

involvement more frequent. In one case from the control group and in four cases from the treated group no atheromas could be found.

The atheromas of both groups were composed of large clear cells with abundant cytoplasm and well-defined cell membranes among which mild round cell infiltration, mostly macrophages, was seen (Fig. 3). No definite increase in capillaries or fibroblasts was noted. In the deeper layers of the larger atheromas the foamy cells tended to gradually lose their cell boundaries, conglutinated, and finally lost their nuclei to form amorphous semitransparent masses in which cholesterol crystals were often seen (Fig. 4). The degree of foamy cell destruction in the two groups is compared in Table III. These changes were more prominent in the control group.

HEART. One heart specimen was lost from each group. The degree of coronary sclerosis was determined by assessing the severity of atherosclerotic change and the thickness of the atheromas. The results are listed in Tables II and III. The degree of coronary sclerosis in the treated group was less than that found in the control group. There were 2 cases in the control group which showed no coronary sclerosis whereas none of the treated group escaped from the formation of coronary sclerosis. The coronary sclerosis was quite different from the atheroma found in the aorta. There was marked thickening of the intima and equally marked narrowing of the lumen. The intima was always replaced by huge clear xanthomatous cells or foamy cells (Fig. 5). In a few cases shadows of cholesterol crystals were seen in the cytoplasm of the foamy cells but none were destroyed as was the case with foamy cells found in the aortic atheroma.

Some cases of small fresh anemic infarcts of the myocardium were seen, but the difference between the two groups was not significant (Table II). However the myocardial fibrosis was more intense and frequent in the control group as shown in Table III. The myocardial fibrosis was usually of a chronic nature and accompanied by only a mild degree of lymphocytic infiltration with no capillaries, acute inflammatory cells, or macrophages (Fig. 6).

PERIPHERAL BLOOD VESSELS. The smaller arteries, such as the arcuate artery of the kidney, hepatic artery in the portal tracts, and arterioles seen in sections of the visceral organs were carefully examined but only rarely were xanthomatous cells or edematous reactions of the intima seen. Hence no comparisons could be made.

Other organs

LIVER. One specimen from the control group was lost. In the treated group, 3 specimens showed no change while the other 9 specimens demonstrated ordinary zonal fat metamorphosis which extended from the central zone to the midzone (Fig. 7), being most marked in the central zone. A mild to moderate degree of lymphocytic infiltration in the portal areas and a few eosinophiles in the narrowed sinusoids was seen. In the control group only 3 out of the 11 specimens demonstrated central zonal fat metamorphosis, while in the other 7 the hepatic cells were markedly distended and pale-staining forming xanthomatous cells not unlike the Gaucher

Table III. Histological findings in aorta and heart

Changes	Control group	Treated group
Thickness of atheroma/thickness of aortic wall		
Over 1	5	2
1:1	6	3
Below 1	0	3
No atheroma	1	4
Destruction of foamy cell in aortic atheroma		
No atheroma	1	4
Foamy cell well preserved	0	2
Foamy cell moderately destroyed	2	1
Foamy cell markedly destroyed	9	5
Coronary sclerosis		
None	2	0
Mild	1	7
Moderate	5	3
Marked	3	1
Myocardial fibrosis		
None	1	6
Mild	6	2
Moderate	1	3
Marked	3	0



Fig. 3. Large atheroma composed of large clear foamy cells and with medial invasion. There is no remarkable foamy cell destruction (treated group).

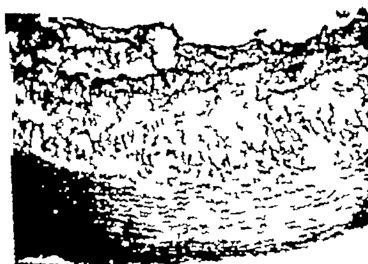


Fig. 4. Atheroma with marked destruction of foamy cells (control group).

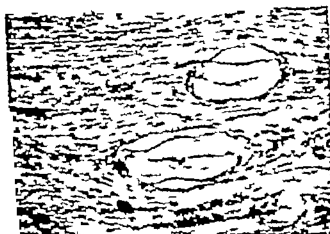


Fig. 5. Marked coronary sclerosis and extreme narrowing of the lumina. Mild round cell infiltration of the myocardium... but there is no necrosis or fibrosis of the myocardium (treated group).



Fig 6 Old m rdial nfarct n with mild round cell infiltration. T the left of the middle sclerotic coronary artery is see



Fig 7 Typical zonal f t metamorphosis around the cent al vein. Slightly enlarged portal area and moderate round cell infiltration was also noted

cells found in Gaucher s disease. This xanthomatous cell change diffusely in volved all parts of the hepatic lobules but in 4 out of 7 this change was prominent only in the central zone (Fig 8) The sinusoids were always indistinct in cases of advanced xanthomatous liver cell de generation The lymphocytic infiltration was also more marked in this type of de generation. One case of the control group showed a mixture of the above two changes.

A mild to moderate degree of fibroblastic proliferation was seen around the central veins in nearly all cases of both groups and mild portal collapse was noted in 8 of 11 cases in the treated group compared to 3 out of 11 cases in the control group. Moder ate bile stasi was found in the portal bile ducts in one case from the treated group and mild intracanalicular bile stasis was found in 4 cases from the control group



Fig 8 The hepatic cords are markedly distorted due to ballooning degeneration or xanthoma cell change of the hepatic cells.



Fig 9 Numerous cholesterol crystals in advanced interstitial edema with xanthomatous cell formation.

KIDNEYS. One specimen from the control group was lost. The kidneys showed only very mild changes. Interstitial edema was first seen in the medula. As the intensity of edema increased foamy cell formation and even destruction of foamy cells with resultant cholesterol crystal formation (Fig 9) could be seen in a few cases. The lining epithelial cells of renal tubules, usually at the distal portion of Henle's loop frequently showed groups of foamy cell degeneration (Fig 10) Other changes were evidenced by the presence of hemoglobin cast formation or proteinous fluid accumulation within the lumen of the renal tubules predominantly the collecting tubules Over half of each group showed a minimal to moderate degree of cast formation The difference between the two groups was not statistically significant. Table IV summarizes the kidney findings.

ADRENAL. Eight specimens from treated group and 6 from the control were examined. In both groups the

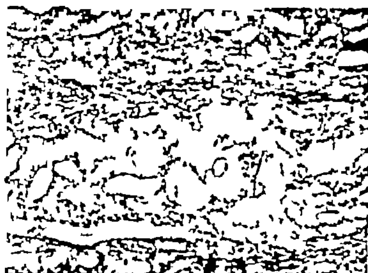


Fig 10 X th atou hange of epithelial cell of renal tubules. The lumina are narrowed and some ery thin proteins fl l he l m na is see

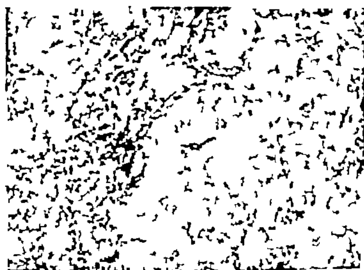


Fig 11 Marked xa thomatous hange nd swelling of adrenal cortical cells on the left. Destruction of these cells to form amorphous nod les with mild RES cell proliferation.

cortical cells showed severe and diffuse xanthomatous changes The sinusoids were always invisible. As the degree of xanthomatous degeneration increased the deeper portion of the foamy cells was gradually destroyed forming amorphous nodules in which abundant macrophage infiltration a few eosinophiles, and a neutrophilic reaction could be seen (Fig 11) Cholesterol crystal formation was seen in the larger of these lesions. There was no significant difference between the two groups

BRAIN Nine specimens from the treated group and 4 from the control group were examined The brain substance and ganglion cells were generally normal, but focal glial cell accumulation was seen in 4 out of 9 cases from the treated group and in 3 out of 4 from the control group. The blood vessels of the brain were all normal and there was no softening or scarring Of note was that nearly all brains showed xanthomatous cell accumulation in the interstitial tissue of the choroid plexus



Fig. 11 Xanthoma cells in the choroid plexus of brain. At upper right ... ther b nda t ro nd ell ... bl r tion ...

Table IV. *Pathologic changes of kidneys*

Kinds of change	Degree	*Control group* (N cases)	*Treated group* (N cases)
Interstitial edema	none	1	2
	mild	6	9
	moderate	4	1
Fatty cell formation	none	2	6
	mild	6	4
	moderate	3	2
Bowman's capsule coat or proteinous fluid in tubular lumen	none	3	5
	mild	6	6
	moderate	2	1

(Fig. 12) These xanthomatous cells could also be broken down, forming cholesterol crystals in a granulomatous inflammation within the plexus but this was seen in only one case from each group and no comparison could be made between groups.

Discussion

It is a new and interesting concept to use a compound with bradykinin-antagonistic property for the prevention and treatment of atherosclerosis without attempting to change plasma lipid metabolism. In our present experiment with rabbits kept on cholesterol feeding, the pyridinolcarbamate-treated group demonstrated a significantly lower incidence ($p < 0.01$) of atherosclerosis, while in both groups the blood cholesterol and total lipids remained at the same level. The pyridinolcarbamate-treated group had a smaller percentage of Sudan IV positive areas on the aorta, less frequent and relatively milder myocardial fibrosis and coronary sclerosis as compared to the control group.

In this experiment the authors could not find a correlation between the surface percentage of aortic fatty streak involvement and the degree of coronary sclerosis or myocardial fibrosis (Table II). Animal No. 580 showed neither fatty streak nor atheroma of the aorta grossly or microscopically but did show rather severe changes of coronary sclerosis and myocardial fibrosis. The reverse situation was seen in Animals 587, 588, and 594. The aorta of these animals showed severe atherosclerotic change but coronary sclerosis and myocardial fibrosis was minimal. A discrepancy was also noted between the percentage of fatty streak involvement of the aorta and the thickness of the atheromas (Animals 577, 584, 587, 588, and 594).

This is the first report which compares the changes noted in parenchymal cells of the liver between cholesterol fed and pyridinolcarbamate treated rabbits. We noticed the former tended toward a diffuse xanthomatous degeneration and the latter toward a zonal fat metamorphosis. The reason for this difference is not known, but we considered that pyridinolcarbamate might have some influence on the enzy

matic system of liver cells or other organs rather than simply being a result of its bradykinin-antagonistic effect.

Finding in some cases from the control group xanthomatous degeneration of the hepatic cell, thick proteinaceous fluid similar to hemoglobin casts in the renal tubules, and glial nodule formation or perivascular cuffing in the brains of a few cases from each group led us to consider the possibility that these changes were due to cholesterol intoxication since extraordinarily high serum cholesterol level were attained during the experiment.

The authors found an edematous arterial reaction of the intima in only a few cases. These cases were included in the group designated as demonstrating weak atheroma formation. Shimamoto and his co-workers demonstrated marked atheroma fibrosis within the pyridinolcarbamate-treated group and considered this to be a healing stage. In our experiment, the only qualitative difference between atheromas from the two groups was the finding that xanthomatous cells in the control group were more frequently ruptured or destroyed, whereas those in the treated group were better preserved.

Atherosclerosis may be present in humans with or without an associated hypercholesterolemia. On the island of Taiwan serum cholesterol levels are relatively low, but the frequency of aortic atherosclerosis at autopsy is similar to that found in the United States although it is of lesser severity.[14] Rocha e Silva[4] discovered bradykinin in pseudoglobulin of normal plasma and found that it was released by venoms and trypsin. Bradykinin has been shown to be a potent factor in increasing capillary permeability, causing vasodilatation and stimulating certain types of smooth muscle.[17] Horton and Lewis[18] described two enzymes which were capable of forming plasma kinin, one acting quickly and the other more slowly. These enzymes were identical to kallikrein and urokinase respectively. Rowley demonstrated that bradykinin increased vascular permeability by initially causing venoconstriction which in turn increased the pressure in the proximal venules and opened the endothelial gaps. On the other hand, a direct mechanism which operated to increase vascular permeability and the partial dissociation of the endothelial sheet was explained by Majno and Palade,[20] who observed an accumulation of chylomicra and enzymes from leaking vessels and widened intercellular junctions.

Vasa vasorum usually extend up to the medial one third of the media of arteries but may, in some species and some portions of the artery, reach the intima. Shimamoto[21,22] postulates that the pathogenesis of atherosclerosis in a large artery is based on a disturbance in the microcirculation induced by bradykinin. The venoconstriction and increased permeability results in the leakage of plasma substances containing lipids and enzymes into the media and even to the subendothelial space. Burch and DePasquale[23] suggested that ischemic myocardial tissue may liberate bradykinin which in turn could produce the pain of angina pectoris. It is interesting that bradykinin constricts sheep coronary vessels and dilates dog coronaries.[5] Other antihistamine and antibradykinin agents were studied but failed to show any antiatherosclerotic effect.[5]

Pyridinolcarbamate has been shown to inhibit the increased permeability and venoconstrictive effect of bradykinin on the vasa vasorum. The authors agree with the opinion that bradykinin plays a most important role in the pathogenesis of large artery atherosclerosis. Nevertheless, the problem still remains as to whether the route of lipid transport into the arterial wall is via the vasa vasorum only or by the vasa vasorum and a direct transfer from the intimal endothelial cell.

Summary

Pyridinolcarbamate was used to prevent atherosclerosis formation in experimental animals.

Twenty-four male albino rabbits were kept on high cholesterol diets for 15 weeks. They were divided into two groups, 12 rabbits for the control group and 12 rabbits for the pyridinolcarbamate-treated group. There was no statistically significant difference between the two groups when serum cholesterol and total lipids were determined. The results are summarized in the following paragraphs.

1. The percentage of aortic fatty streak

involvement was significantly different between the two groups 12.7 per cent for the treated group and 37 9 per cent for the control group ($p < 0\ 01$) The degree of foamy cell destruction in aortic atheromas was greatest in the control group

2. Myocardial fibrosis and coronary sclerosis was less frequent and milder in the pyridinolcarbamate-treated group The difference in fibrosis between the two groups was statistically significant at a level of $p < 0.05$.

3. The pyridinolcarbamate treated group showed zonal fat metamorphosis in the liver while the control group demonstrated a diffuse xanthomatous degeneration. The reason for this difference is not understood

REFERENCES

1. Weinhouse, S and Hirsch E. F Chemistry of atherosclerosis Lipids and calcium content of the intima and of the aorta with and without atherosclerosis, Arch. Path. 29:31 1940.
2. Anitschkow N and Chaltow S. Ueber experimentelle Cholesterinsteatose und ihre Bedeutung fur die Entstehung einiger pathologischer Prozesse, Zent. bl. f. allg Path. 24 1 1913.
3. Keys, A.: Diet and the epidemiology of coronary heart disease, J A. M A. 164 1912, 1957
4. Virchow R., Der atheromatoese Prozess der Arterien, Wien. med. Wchnschr 6:809 825 1856 Cited by Pollak.
5. Beck, H. Entzundung und Sklerose der Lungenschlagader-Ein Beitrag zur Kenntnis des Begriffes und der Erscheinungsformen der Endarteriitis and Arteriosklerose, Virchows Arch. Path. Anat. Phys. 308:60 1942.
6. Pollak, O. J Etiologic concept of atherosclerosis based on study of intimal alterations after shock, Circulation 5:539 1952.
7. Shimamoto, T: The relationship of edematous reaction in arteries to atherosclerosis and thrombosis, J Atheroscler Res. 3:87 1963.
8. Shimamoto, T and Sunaga, T Edematous arterial reaction by adrenalin and cholesterol and its prevention by MAO inhibitor observed by electron microscopic technique Jap. Heart J 3:581 1962.
9. Shimamoto, T Fujita, T Ishioka, T., and Sunaga, T Treatment of experimental and human atherosclerosis with pyridinolcarbamate, Acta M. J 8:12, 1965.
10. Shimamoto, T Numano, F and F Jita, T Atherosclerosis-inhibiting effect of antibradykinin agent, pyridinolcarbamate, Am. Heart J 71:216, 1966.
11. Shimamoto, T Maezawa H., Yamazaki, H Atsumi, T F Jita, T Ishioka T and Sunaga, T Pyridinolcarbamate, a bradykinin antagonist in ... ems, Am. Heart J 71:297 1966.
12. Gradwohl, R. B H.: Clinical laboratory methods and diagnosis, vol. 1 St. Louis, 1956, The C. V Mosby Company p. 365.
13. Kunkel, H G Ahrens, E. H., J and Eisenmenger W J Application of turbidimetric methods for estimation of gamma globulin and total lipid to the study of patients with liver disease, Gastroenterology 11:499 1948
14. Tsai H. C W C. C and Chen J S Cholesterol level in patients of coronary atherosclerotic heart disease, J Formosa M A. 61 1031 1962
15. Yeh, S. Some geographic pathology aspects of common disease in Taiwan, Internat. P th 6:81 1965
16. Rocha e Silva M Beraldo, W T and Rosenfeld, G. Bradykinin, a hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin, Am J Path. 156:261 1949
17. Elliott, D F Horton E W and Lewis, G P Action of pure bradykinin J Physiol 153:473 1960.
18. Horton, E. W and Lewis G P A comparison of the plasma kinin forming enzymes in urine kallikrein and urokinase, J Physiol 149:477 1959
19. Rowley D A Venous constriction as the cause of increased vascular permeability produced by 5 hydroxy tryptamin, histamine bradykinin and 48/80 in the rat Brit J Exper Path 45:56, 1964.
20. Majno, G. and Palade G. E. Studies on inflammation The effect of histamine and serotonin on vascular permeability an electron microscopic study J Biophys. & Biochem Cytol. 11:571 1961
21. Shimamoto, T Our search for an anti-atherosclerotic drug: Pyridinolcarbamat microcirculatory aspects of therogenesis and thrombogenesis, in Gabbiani, Giulio editor: Reflection on biologic research, St. Louis, 1967 Warren H Green, Inc. p 191
22. Shimamoto, T Microcirculatory aspects of therogenesis, thrombogenesis, nd antiatherosclerotics, Am Heart J 76:105 1968.
23. Burch, G E., and DePasquale N P Bradykinin Am. Heart J 65 116, 1963
24. Kovalcik, V: Effect of bradykinin on isolated coronary arteries, N ture 196:174, 1962.
25. Harman, D Inhibiting effect of an antihistaminic drug chlorphentramine, Circulation Res. 11:277 1962.

Case reports

Concealed right bundle branch block in the presence of Type B ventricular pre-excitation

W lton M Ger ony M D
Dorothy D Ek r M D
D lla T x

Types A and B of the Wolff Parkinson White syndrome (WPW) were originally described by Rosenbaum and associates on the basis of delta wave polarity in the precordial and esophageal leads of the electrocardiogram (ECG). Hecht[2] and Latour and Puech later postulated that the pre-excitation area is in the left ventricle for Type A and in the right ventricle for Type B. Recently Durrer and Roos demonstrated by direct measurement with epicardial leads that pre-excitation in Type B did actually occur in the right ventricle as previously theorized. This data has been used to support the concept of an accessory muscle bundle outside of the conduction system connecting the right atrium and right ventricle as the etiology of Type B WPW. If the hypothesis is correct the presence of right bundle branch block (RBBB) should be obscured by Type B WPW because of pre-excitation of the right ventricle distal to the block. On the other hand in apparent opposition to the accessory pathway theory ECG material has been published which indicate that these 2 entities do indeed occur together.[5-8] These reports could be interpreted as favoring an alternate theory of the origin of WPW one that would postulate pre-excitation to result from the abnormal structure or function of the conduction system itself.[5,8]

A patient in whom RBBB disappears completely during a period of Type B pre-excitation is described in this communication and the significance of this occurrence is discussed in the context of the anatomic basis of these lesions.

Case report

S L, a 10-year-old Negro boy was admitted to Children Medical Center Dallas, Texas on March 30 1966 because of dyspnea on exertion and nocturnal dyspnea of one year duration. The boy was not known to have heart disease in the past and the parent denied any significant symptomatology related to the cardiovascular system. The patient had been obese since infancy and his mental development had been considered to be low.

Physical examination on admission revealed an obese boy who did not appear to be acutely ill. The height was 53 ½ inches (twenty-fifth percentile for age), and the weight was 114 pounds (over the ninety-seventh percentile for age). The blood pressure was 110/90 in the right arm and 110/70 in the left leg. The heart rate was 84 beats per minute, and respirations were 24 per minute. The mucous membranes were plethoric and slightly cyanotic and there was minimal clubbing of the fingers and toes. The lungs were clear to auscultation the liver was

From the Department of Pediatrics, Children Medical Center University of Texas, Southwestern Medical School, Dallas Texas.
This study was supported in part by the Southwestern Medical Foundation, Fred and Louise McClarkin Fund.
Received for publication Feb 13 1968.
*Present address. Department of Pediatrics, College of Physicians and Surgeons of Columbia University, 630 W. 168th St., New York, N. Y. 10032.

May 1969 Vol. 77 No. 5 pp. 668-6

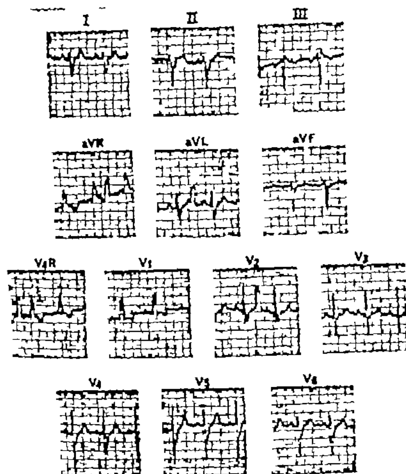


Fig 1 ECG taken on initial admission of March 30 1966. QRS interval measures 0 16 second with configuration of RBBB QRS axis is −120 degrees. The P R interval is 0.20 second.

enlarged and the spleen was not palpable. The pulses were full and equal over the 4 extremities. Cardiac examination revealed a quiet precordium with a faint right ventricular impulse. The first sound was normal at the apex, and the second sound was constantly split along the left upper sternal border. There was a Grade II/VI blowing pansystolic murmur which was heard best along the left lower sternal border and radiated toward the apex. The remainder of the physical examination was within normal limits.

Laboratory data: the hemoglobin was 17.5 Gm. per cent, hematocrit 53 per cent, white blood count normal, and urinalysis were normal. The chest roentgenogram showed nonspecific cardiac enlargement with increased pulmonary vasculature. The ECG (Fig 1) revealed a frontal plane axis of −120 degrees and complete RBBB. The vectorcardiogram (Fig 2) showed a superiorly oriented, wide counterclockwise loop in the frontal plane. The horizontal view revealed completely anterior forces with terminal slowing of the clockwise vector loop. There was no delay of the initial QRS vector.

After initial evaluation, the diagnosis of endocardial cushion defect was entertained, and cardiac catheterization was carried out on March 31 1966. The findings included atrial septal defect and left superior vena cava emptying into the coronary sinus, which in turn communicated to the left atrium (partial anomalous systemic venous return). A bidirectional shunt at the atrial level was found and there was no pulmonary artery hypertension. An intracardiac electrocardiographic study was not suggestive of His-system abnormality.

Cardiac surgery utilizing cardiopulmonary bypass was carried out on May 3 1966. The findings included left superior vena cava and coronary sinus emptying into the left atrium, large atrial septal defect and left mitral and tricuspid valves. The tricuspid valve was not malpositioned. The valvular defects were repaired, and an Ivalon patch was sewed over the common atrioventricular (A V) valve ring so as to form a conduit from the left superior vena cava and coronary sinus to the right atrium. Suturing was continued along the upper border of the atrial septum closing the septal defect. Except for

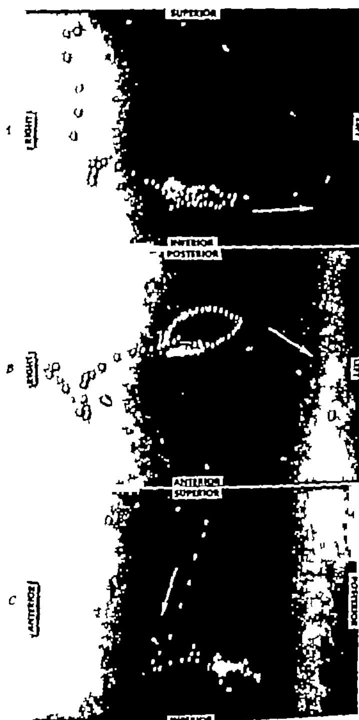


Fig 2 Frank vectorcardiogram A frontal B horizontal, and C, sagittal views. There is superior oriented counterclockwise loop the frontal plane and the horizontal view shows the entire loop to be oriented anteriorly. There is marked terminal delay indicative of RBBB.

2 bouts of supraventricular tachycardia which abated spontaneously the patient had an uneventful recovery period. The postoperative ECG continued to show RBBB

On May 16 1966 routine ECG (Fig 3) revealed the presence of WPW syndrome Type B with evidence of RBBB The configuration of the P waves had changed significantly. The variation in contour was particularly apparent in Leads III aV and V All subsequent ECG's including one taken during an episode of supraventricular tachycardia (Fig 4) have shown only complete RBBB with the

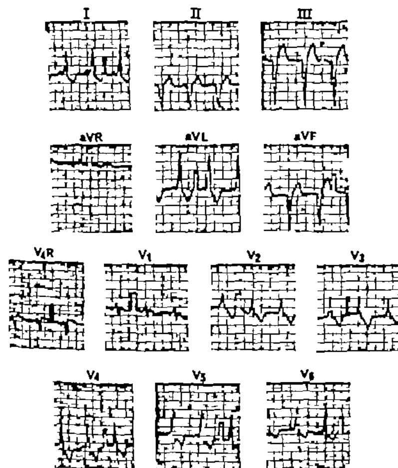


Fig. 3 The above tracing was taken during an episode of Type B WPW. The QRS interval has become shorter (0.12 second), and the later rightward forces seen with RBBB have completely disappeared. The P-R interval measures 0.10 second, and delta waves are prominent in all of the leads. Note the QS pattern in Leads II, III, aVF, and V1, classical of Type B pre-excitation.

configuration of the P waves similar to those in the original ECG. The patient has remained asymptomatic since surgery except for rare attacks of paroxysmal atrial tachycardia.

Discussion

Durrer and Roos[4] directly demonstrated the pre-excitation area in Type B WPW to be in the right ventricle. These authors recorded epicardial excitation during surgery for a secundum type atrial septal defect in a patient with Type B WPW. Early activation was noted at the right lateral cardiac border near the A V sulcus in an area corresponding to that described in anatomic studies[11] as the location of a muscular bypass between the right atrium and right ventricle. Burchell and colleagues,[12] by means of epicardial exploring electrodes, also found early excitation of the right ventricle at the A V groove in a patient with Type B WPW. Both groups of investigators added support to the concept of an A V muscle bundle (Kent) as the basis of the WPW syndrome in their cases.

Within the framework of this experimental evidence, the occurrence of Type B WPW with left bundle branch block (LBBB) and of Type A WPW with RBBB in the same ECG is easily understood. The pre-excitation area is in one ventricle and the involved bundle branch is in the

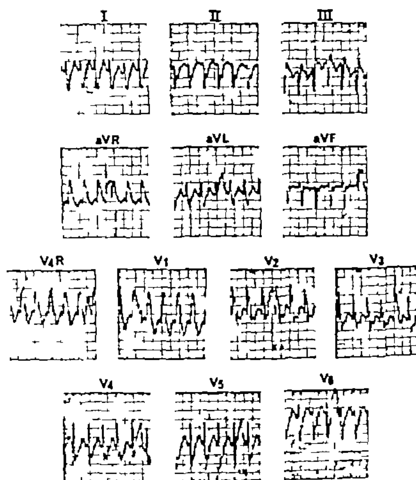
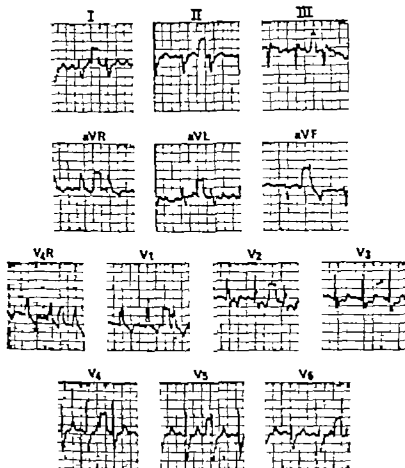


Fig 4 1 ECG ken on F 1 20 1967 d ring a episode of upra entricular tachycardia. QRS configura remains that of RBBB

contralateral ventricle Ventricular de polarization i i fluer ced by both and the QRS vector shows initial features of WPW and the terminal slowing of bundle branch block. If the postulated location of the pre-excitation area in the right ventricle is correct theoretically the simultaneous features of Type B WPW and RBBB should not occur since pre excitation of the ipsilateral ventricle should bypass the right bundle and thereby mask RBBB Gamboa and co-workers[13] supported this thesis by experimentally in ducing RBBB by catheter stimulation of the ventricular septum in a patient with intermittent Type B WPW The presence of RBBB was disclosed only during ven tricular activation without pre-excitation It was concluded that because ventricular depolarization was dependent on the n ventricular pre-excitation phenomen RBBB did not alter the end of ventric activation in Type B WPW Kedi : Wennemark[14] described a related p nomenon utilizing a similar method Th workers produced WPW by stimulat the ventricular septum at catheterizat This would support the concept of accessory AV pathway by the assu tion that complete blocking of nor conduction through interference by catheter could lead to AV conduct by such aberrant pathways if they present

Experimental evidence notwithstand Type B pre-excitation and RBBB h been described as occurring simultaneo in several reports.[1-4] It is of importance



(2 20-67)

Fig. 4. B ECG of Feb. 20, 1967. Sinus rhythm, 1 degree A-V block, and complete RBBB after cessation of an episode of supraventricular tachycardia.

note that in all but one instance[8] the patient also had Ebstein's disease. A possible answer to the apparent paradox of Type B WPW and RBBB in Ebstein's anomaly may be provided by histological evidence that the right bundle is not interrupted in these patients even in the presence of right ventricular conduction disturbances.[14] Since in all probability most cases of Ebstein's do not have central block of the right bundle but rather delay in peripheral conduction through abnormal right ventricular myocardium, simultaneous right bundle branch system block and Type B WPW in these patients should not be construed as evidence against the theory of localization of Type B WPW in the right ventricle.

Zakopoulos and associates[8] described a 70-year-old man with paroxysms of tachycardia who was said to have Type B WPW and RBBB in the absence of congenital heart disease. On careful scrutiny of the ECG, however, the QRS duration was 0.09 second prior to the occurrence of WPW. A RBBB configuration and QRS duration under 0.12 second may result from block distal to the region of the main bundle. Uhley and Rivkin[7] interrupted the peripheral branches of the right bundle in dogs and noted no significant QRS prolongation, but only a change in direction of the terminal forces. They suggested an analogy between this experimental model and localized defects in the peripheral conduction system in man, resulting in a change in QRS contour without significant QRS prolongation. Zakopoulos and as-

4. D urrer D ad Roos J I Lpic rdial exc t tion of the ve tricles patient with Wolff Parkinson Wh t ndrom (T pe B) Circulation 35 15 1967
5. Cabrera, E F ldm J nd Ol to, I C. Estudio Ele tro Vectoc rd g fico un caso de Wolff Park s Wh t con bloqueo de rama derecha Arch I t C rd M 29 101 1959
6. Roberts I C C I le-Sm th D Lowe K C nd W H The s sation of T pe B vent k pre t nd ight bundle br h bl k B H t J 25 735 1963
7. C brer I E A V I rr I nd C st Rocha J Ab the IV World Congress of Card l g M 196 p 50
8. Z kope K K I V Eh nd Lukas T I I pe B W lff P k son Wh t ndrome ssociat d h igh bu dle b nch block, Dis Chest 46 346 1964
9. P zma l M K er R C rda I Osborne J V I ield J I Sm th I V Vec ler t d nd C New Y k 1952, Grune & S tton Inc p 68
10. Sherf I d J nes I V A new look t some old q est I I k m rocarding ph Henry Ford Hosp Med B ll 14:265 1966
11. W d I C W lferth C C nd Geck ler C D Histol g dem st t n of accessory m s l k s betwee uricle nd en t k se d h t I R inters l nd prolong d QRS omple Am H t J 25 454 1943
12. B rchell H B I R I Anderson M W nd M C D C A sventric lar nd ventric l l t tion W olff Parkinson Wh t nd ome T pe B) Circ lation 36:663 1967
13. C m R I ako D Some I nd Ba ber V The le of the right nd left ventricles the tric lar pre-excit tion (WPW) ndrome Am J C rdiol 10:650 1962
14. Kerdi, I and Wennemark J Ebstein malformation Clinic l findings and hemodynamic alterations, Am J Card l 2:200, 1958
15. Y ter W M and Shapiro, M J Congenital displacement of the tricuspid valve (Ebstein's disease) Review and report of case th ele trocardium abnormalities and histologic study of the conduction y tem, Ann Int Med 11 1043 1937
16. Lev M Gibson, S., and Miller R. A. Ebstei disease with Wolff Parkinson-White yndrome Report f case with histopatho logic tudy of pos ible conduction pathways Am. Heart J 49 724 1955
17. Uhley H N and Rivkin, L. Electrocardiographic pattern following interruption of main nd peripheral br nches of the canine right bundle of His, Am. J Cardiol. 7:810, 1961
18. Wolff L., and Richman, J L. The diagnosis of myocardial inf rction in patient ith anomalous triovent icular excitation (Wolff Parkinson-Wh te yndrome) Am Heart J 45:545 1953.
19. Lev M Leffler W B Langendorf, R and Pick A. Anatomic findings in a case of ventricular pre-ex it tion (WPW) terminating in complete triosventricular block, Circulation 34 718, 1966.
20. Pick, A nd Fisch, C Ventricular pre-excitation (WPW) in the presence of bundle branch block, Am Heart J 55:504 1958
21. Varriale I Alfen to, J and Kennedy R J The im lt neous occurrence of entricular pre-excitation, left bundle branch block, and delay of A V conduction Am Heart J 71:803, 1966
22. Cast llanos A J Mayer J W and Lemberg L The electrocardiogram and ectorcardiogram in Wolff Parkinson-White yndrome associated with bundle br nch block, Am J Cardiol 10:657 1962

Spontaneous rupture of a false left ventricular aneurysm following myocardial infarction

Robert A Ersek M.D
Elliot Chesler M B M R.C P (Edin)
Michael E. Korns M.D
Jesse E. Edwards M.D
Minneapolis Minn

Rupture of an aneurysm of the left ventricle is uncommon Mycotic and traumatic aneurysms have a tendency to rupture[1,2] but rarely is this complication observed with the usual type of aneurysm of the left ventricle which is a sequel of myocardial infarction.[3-4]

This communication reports the findings in a case of healed myocardial infarction in which fatal hemopericardium resulted from rupture of a false aneurysm of the left ventricle.

Case report

Without past history of cardiac disease, a 73-year-old man complained of sudden onset of severe substernal pain which radiated to the jaw The pain was persistent and was accompanied by shortness of breath and palpitations Physical examination revealed an acutely ill patient whose blood pressure was 170 mm. Hg systolic and 80 mm. Hg diastolic The pulse rate was 150 beats per minute and was regular There was no evidence of congestive cardiac failure.

On admission, the roentgenograms of the thorax were normal apart from prominence of the ascending aorta, the electrocardiogram (ECG) revealed atrial fibrillation. This subsequently reverted spontaneously to sinus rhythm (Fig 1). Abnormal Q waves accompanied b elev tion of the S-T segment were prese t n Lead V and tandard Lead III Abnormal Q w es were lso presen t dard Lead II nd V the T w es were verted st ndard Leads II nd III and V ad V These find ng were considered compatible w th ac te posterolateral myocardial inf rction

The patient w treated th ticoagula t and sedatives H died udde l on the second hospital day

Pathologic feat es The pericardial sac w tight distended w th blood and there were no adhesion between the parietal pericard m nd epic rd um The cause of the hemopericard um wa ruptured neury m situated on the posterior rface of the left ventricle nea its pe The neurysm was oval nd measured approximately 7 by 5 cm. in ts greatest dimension A ragged perforation, pprox mately 2 5 cm length, wa prese t on the anterior surface of the neurysm near ts pex (Fig 2,A nd B)

A transverse section through both entricles nd the neurysm showed n brupt transition from the thick w ll of he left ventricle t the thi wall of the neurysm The wall of the aneurysm wa only 2 mm hick and consisted of friable gray fibrous tissue The neurysm as lined by laminated thrombus except t he sit of perforation (Fig 3)

The coronary arteries showed a severe degree of therosclerosis org nizing thrombus was present the proximal portion of the right coronary artery Histologically sections from the junction of the

From the Department of Pathology The Charles T Miller Hospital St. Paul Minn and the Departments of Pathology Medicine, and Surgery University of Minnesota Minneapolis Minn
This study was supported by Public Health Service Research Grant 5 RO 1 HE05694 and Research Training Grant 2 T HE05570 from the National Heart Institute
Received for publication Feb. 29 1968.
Address Pathology Department, The Charles T Miller Hospital, 25 West College Avenue, St. Paul, Minn. 55 01

left entricle and the neu howed n abrupt termination of ardiac m scle t became continuous w th the w ll of the ne rysm the latter wa formed by mi ture of de se f brou nd granulation tissue lam nated org ng th ombus present the cavity of the ne rysm w different to the lin ng (Fig 4).

The endocardial half of the rd near the mouth of the aneu m exhib d glomer t scars which were terpreted ej t q he led myocardial inf rction N nect t le w present. The epicard um er the nd over the adjacent left ul w ll h wed org ng fibrinous peric rd tis

Comment

In the usual instance of aneurysm of the left ventricle following myocardial infarction the aneurysm is of the true variety In this type of aneurysm the wall is constituted by elements of the infarcted left ventricular myocardium and represents a bulging of a weakened wall Usually the wall has sufficient surviving muscle fibers and fibrous tissue to withstand the high pressure in the left ventricle In addition,

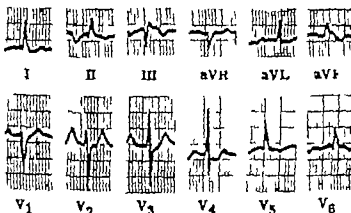


Fig 1 ( ) ion Changes ndic te acute posterolateral myocardial infarction

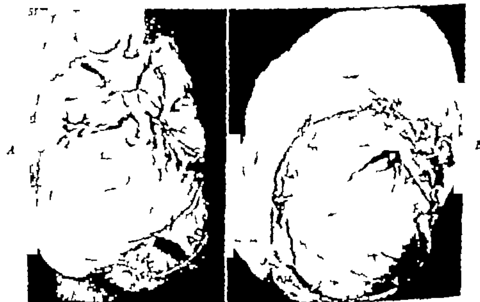


Fig 2 A Exterior of the heart viewed from a left-anterior position. False aneurysm (F An) of left ventricle bulges postero-inferiorly B Exterior of the heart from inferoposterior view in which the false aneurysm is seen "head on. The wall of the false aneurysm of the left ventricle has, in part, been dissected away (arrow) to expose the thrombus within the aneurysm The site of perforation is indicated by letter P



Fig. 3. Oblique section through ventricular portion of the heart revealing the interior of the infundibulum of the right ventricle (R.V.) and the interior of the left ventricle (L.V.). The false aneurysm (F.A.) communicates with the cavity of the left ventricle by way of rupture of the wall of the latter chamber at its apex. Scar tissue is present in the left ventricular myocardium at each side of the site of rupture. Areas in rectangles illustrated as photomicrographs in Fig. 4.

some measure of protection against rupture is probably afforded by a buttressing action of the parietal pericardium which is frequently partially adherent to a true aneurysm.

In contrast in our case the aneurysm is of the false type. Such aneurysms are a result of rupture of the left ventricular wall. Usually rupture of the left ventricle leads to a fatal hemopericardium. If, however, pericardial adhesions are present the hemorrhage may be contained by an adherent pericardium. Subsequent organization of this pericardial hematoma leads to the formation of a fibrous-walled false aneurysm.

The unusual nature of the false aneurysm in our case relates to the fact that the parietal pericardium was not adherent to the aneurysm, so that the false aneurysm lay within the epicardium.

Our interpretation of the sequence of events leading to the state found at necropsy are given schematically in Fig. 5.

Briefly, these are as follows. Although the final illness of the patient was interpreted as acute myocardial infarction, this was proved to have been otherwise. It is assumed that the myocardial scarring was a sign of an attack of acute myocardial infarction in the past and of which no history was given by the patient (Fig. 5 a). As part of the acute stage of the myocardial infarction, the left ventricular

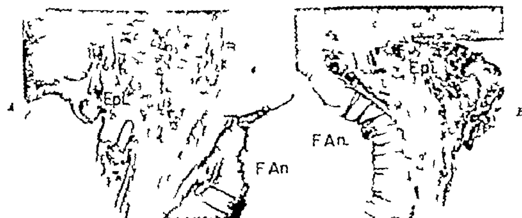


Fig. 4. A and B. Low power photomicrographs of the left ventricular wall as it joins the mouth of the false aneurysm. Areas sectioned indicated within rectangles in Fig. 3. The myocardium, as it joins the mouth of the false aneurysm (F.An.) ends abruptly and is scarred. The aneurysm wall is fibrous. In one area it abuts upon the surface of the epicardium (EpL). (Each hematoxylin and eosin ×7.)

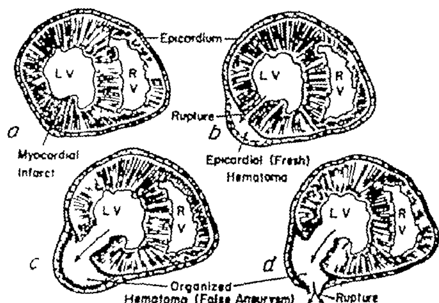


Fig 5 l h d s ed illust ted diagrammatically a Acut my c rdial infarction in the pst b R p c k s ll relation t acut n yocardial infarct Hemorrhage from ruptured heart c c l w l ll t n ng tes t form fibrou wall of f lse neurysm d Bleeding from f lse ll l m ted n mount uddenly became massive t cause mass e hemo perc l f h

t x t h l t g t l but the result n g l t t n l within the ep r l l l he ont ined epi ard l l l t l be organized to res lt in th (F g 5) Bleeding from th f lse n ir appears to have bee ı t r per l of t s evidenced b the prese t x nzing fibrinous pers r lit

The t pt h h beg in 2 days before de th t l w l h w re misinterpreted as s gn f ut m rdi l infarction were probabl used b the onset of bleeding ı to th peric rdiu Bleeding which initially must h e been of limited exte it suddenly bec ime m issive to result in the massive he opericardiu ı (Fig 5,d) and the sudden death

Summary

In a case of m oc irdial infarction rupture of the left ventricle resulted in the formation of ı f lse ane ıysm The aneurysm differed from th t usually found in cases of myocardi l infarction in that its wall was for ied ent rely by fibrous tissue

W wish to acknowledge the ssist nce of Drs Kenneth B. Romness, Charles Carlson, and Rudolf W Koucky

REFERENCES

1 Pitts, H H nd Purves, G S. Ruptured traumatic neurysm n a ch'ld, Canad. M A J 57 165 1947
2 Emans, C L. Erosive (mycotic) neurysm of the heart w th rupture Arch Path. 36:379 1943
3 Schlichter J H llerstein, H K nd Katz, L N Aneurysm of the heart correlative tudy of one hundred nd tw proved cases, Medicine 33:43, 1954
4 Phares, W S Edwards, J E., and Burchell, H B C rdiac neurysms, Clinicopathologic t dies, Proc Mayo Clin 28:264, 1953.
5 Dubnow M H Burchell, H B., and Titus, J L Postinfarction ventricular neurysm A l iconorphologic and lectrocardiographic study of 80 cases, Am He rt J 70 753, 1965.
6. Cone R B., nd Hawley R L. Pseudoaneurysm of the heart following infarction, Arch. Path. 77 166, 1964
7 Riederer T nd Themel K G. Zur Diagnose und Differentialdiagnose eines Herzwand-aneurysmas m t Ruptur nd Pseudodivertikelbildung des Perikards, Cardiologia 27:44, 1955
8. Hurst C O Hoe, G., nd Keyes J W Pseudoaneurysm of the heart Report of se and review of l terature Circulation 28:427 1963.
9 Roberts, W G and Morrow A C Pseudoaneurysm of the left ventricle A unusual sequel of myocardial inf rction nd rupture of the heart, Am J Med 43:639 1967
10. Bjornson L Pseudoaneurysm of the left ventricle of the heart. A r re complication of myocardial rupture following infarction—report of a case, Am. J Clin. Path. 41:302, 1964

Papillary muscle fibrosis in primary myocardial disease

Frank I. Marcus, M.D.
*Lucia Gomez, M.D.***
D. Luke Glancy, M.D.
*Gordon A. Ewy, M.D.**
*William C. Roberts, M.D.*****
Washington, D. C., and Bethesda, Md.

Papillary muscle dysfunction due to coronary occlusive disease is now well recognized.[1-3] Other causes of dysfunction or fibrosis of the papillary muscles include origin of the left coronary artery from the pulmonary artery,[4] endocardial fibroelastosis,[5] and left ventricular hypertrophy of diverse etiology.[2] This report describes fibrosis of the posteromedial papillary muscle of the left ventricle of a 44-year-old Negro woman with primary myocardial disease.

Case report

S. A. was admitted to the Washington Hospital Center at the age of 39 because of an incomplete abortion. At that time she had no history, symptoms, or signs of heart disease. Her blood pressure was 130/80 mm. Hg and the heart was of normal size on chest roentgenogram (Fig. 1, left). At the age of 41 she had the acute onset of pulmonary edema. Thereafter she had repeated episodes of congestive heart failure requiring ma hospital admissions. At each hospital admission the bl d pressures were in the range of 120/90 to 130/100 mm. Hg. [illegible] trial and ventricular diastolic gallops were heard. There was a Grade 3/6 or 4/6 pansystolic murmur heard best at the apex. On several occasions during her last year of life, an additional pansystolic murmur could be identified. This murmur was heard maximally at the fourth left interspace and was considered to be a functional tricuspid murmur. Usually the intensity of the apical pansystolic murmur interpreted as being due to mitral regurgitation, decreased with treatment to Grade 1/6 or 2/6. On several occasions, the apical systolic murmur was noted to end before the second sound closure. Electrocardiograms consistently showed sinus rhythm, left axis deviation, and an intraventricular conduction defect (Fig. 2). Despite salt restriction, diuretics, and digitalis, the heart remained large (Fig. 1, right).

Her last admission was to the District of Columbia General Hospital because of a generalized skin eruption and confusion. She   [illegible] lcoholic and had been admitted to another hospital 6 weeks before because of an epileptic seizure. Discharge medica-

From the Georgetown University Medical Division, District of Columbia General Hospital, the Washington Hospital Center, Washington, D. C., and the Section of Pathology, Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md.

Received for publication March 18, 1968.

*Associate Professor of Medicine, Chief of Cardiology, Georgetown University Medical Division, District of Columbia General Hospital.

**Division of Cardiography, Georgetown University Hospital.

***Staff Associate, Section of Pathology, Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md.

****Associate Cardiologist, Georgetown University Medical Division, District of Columbia General Hospital.

*****Chief, Section of Pathology, Clinic of Surgery, National Heart Institute, National Institutes of Health, Bethesda, Md.



Fig. 1. Che ... before de th. There w no evidence of he rt disease at that time. The rd ic ... before de th. Marked cardiomegal is present.

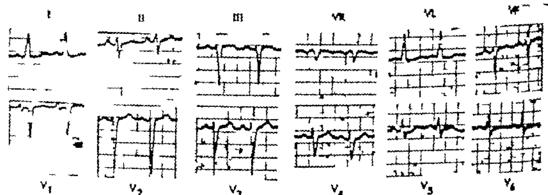


Fig. ... recorded one ... before de th showing normal sinus rhythm, left axis deviation, and ... onduc ion defect.

tions had ... phenobarbital ... The sk eruption was belie ed ... one of these medications.

The blood pres w 120/80 mm Hg, pulse 120 per m ... nd temper ture 103° F. The jugular ... pres re w normal. The left ventricula ... present t the fifth inter space in the ... llary line. The first and second heart sounds were single, nd both trial and ventricular g llops were heard. A Grade 2/6 systolic murmur was he rd over the precord um. The whit blood cou t w 11,200 per cubic millimeter and the differential blood s ear showed 40 per cent eosinophils. Cult res of sput m blood and urine were negative. Despit the withdrawal of all drugs, the fever and skin rash persisted nd she died suddenly on the third hospital day.

A topsy showed bronchopneumonia, pulmonary emboli t the small branches of the right lower lung, port l cirrhosis nd encephalomalacia of the right basal ganglia.

The heart weighed 350 grams. The pericardium, cardiac valves, nd extramural coronary arteries were entirely were norm l. The coronary arteries were free of plaques. The right ventricular cavity as considerably dilated. The left ventricle wa only mildly dilated. The tria were of normal size. The right entricular wall measured up to 0.6 cm. and the left ventricula wall up t 0.9 cm. in thickness. The myocardium of the right ventricle was free of scars. The posteromedial papillary muscle of the left entricle wa atrophied d extensively scarred (Figs. 3, 4 nd 5). The free wall of the left entricle just beneath this papillary muscle was also focally fibrotic. In contrast, the anterolateral papillary mus-



Fig. 3. Opened left ventricle (L.V.) and aortic valve (A.V.). The posteromedial (P-M) papillary muscle is scarred and atrophied. In contrast, the anterolateral (A-L) papillary muscle is large and free of scars.



Fig. 4. Photomicrographs, each taken at the same magnification (X3), of histologic sections through the thickest portions of the anterolateral (A-L) and posteromedial (P-M) papillary muscles (enclosed by dashed lines) of the left ventricle. The anterolateral muscle is twice as thick as that of the posteromedial. Only a portion of the free wall of the left ventricle beneath the anterolateral papillary muscle is included in the photomicrograph. In contrast, the entire free wall beneath the posteromedial papillary muscle is included in the photomicrograph. Hematoxylin and eosin sections on each.

...le was large and free of scars (Figs. 3, 4, and 5). There was no evidence of fibrosis or mononuclear infiltrates in the remainder of the left ventricle.

Histologic examination of sections of heart disclosed large areas of interstitial and replacement fibrosis in the posteromedial papillary muscle and in the left ventricular free wall just beneath it. No inflammatory cells or Aschoff bodies were observed and the intramural coronary arteries were normal.

Comments

This woman had myocardial disease of unknown origin (primary myocardial disease) for at least 3 years. The excessive intake of alcohol may have caused or contributed to the myocardial disease. The mild elevation of the diastolic blood pressure following the onset of cardiac symptoms appears to be of no etiologic significance. The blood eosinophilia, present terminally, is not believed to be related to the cardiac disease. Infiltrative myocardial diseases such as sarcoid, hemochromatosis, or amyloidosis were not found at autopsy, and both the extra- and intramural coronary arteries were entirely normal.

Pathological examination of the hearts of patients with primary myocardial disease usually show myocardial hypertrophy, varying degrees of interstitial myocardial fibrosis, and focal destruction of muscle fibers.[11] The fibrosis may produce intraventricular or bundle branch block. The subject of this report had an intraventricular conduction defect. In addition, a large area of fibrosis involved the subendocardial portion of the left ventricle just beneath and including the posteromedial papillary muscle (Figs. 4 and 5). In contrast, the anterolateral muscle was large and free of scars (Figs. 4 and 5). Although papillary muscle fibrosis has been reported in Duchenne's muscular dystrophy[12] and in sarcoid,[8] it has not previously been noted in idiopathic primary myocardial disease.

In our patient, functional impairment of the posteromedial papillary muscle of the left ventricle appears to have been present and may have been responsible for the mitral regurgitation. Since mitral regurgitation is common in patients with primary myocardial disease in the absence of papillary muscle fibrosis,[8] u-u.n. i. a. the association between the pathological finding papillary muscle fibrosis and clinical fin...



Fig. 5. Sections of portion of each of the papillary muscles. Each photomicrograph is taken at the same magnification (×65). Left: Portion of the anterolateral papillary showing hypertrophy of the myocardial fibers but no scarring. Right: Portion of posteromedial papillary muscle showing extensive scarring. Most of the myocardial fibers which remain are located at the periphery of the papillary muscle. Hematoxylin and eosin stains on each.

of mitral regurgitation must remain speculative in our patient. Papillary muscle fibrosis nevertheless should be considered a possible cause of mitral regurgitation in patients with primary myocardial disease.

Summary

A 44-year-old woman with primary myocardial disease was found to have fibrosis of the posterior papillary muscle of the left ventricle. The fibrosis also involved the free wall of the left ventricle just beneath this papillary muscle. In patients with primary myocardial disease who have a mitral insufficiency, papillary muscle fibrosis should be considered as a possible cause of this murmur.

We are indebted to Dr. James Bacos, Chief of Sub-Department of Cardiology, Washington Hospital Center, for permission to review the extensive hospital records of this patient. We wish to thank Mrs. Yvonne M. Daaia for secretarial assistance and Mr. Bernard Salb of the Department of Medical Communications, Georgetown University Hospital.

REFERENCES

1. Heikkila, J.: Mitral incompetence complicating acute myocardial infarction. Brit. Heart J. 29:162, 1967.
2. Bashour, F. A.: Mitral regurgitation following myocardial infarction. The syndrome of papillary mitral regurgitation. Dis. Chest. 48:113, 1965.
3. Phillips, J. H., Burch, G. E., and DePasquale, N. P.: The syndrome of papillary muscle dysfunction. Ann. Int. Med. 59:508, 1963.
4. Noren, C. R., Raghib, G., Moller, J. H., Amplatz, K., Adams, P., Jr., and Edwards, J. E.: Anomalous origin of the left coronary artery from the pulmonary trunk with special reference to the occurrence of mitral insufficiency. Circulation 30:171, 1964.
5. Moller, J. H., Lucas, R. V., Jr., Adams, P., Jr., Anderson, R. C., Jorgens, J., and Edwards, J. E.: Endocardial fibroelastosis. A clinical and anatomic study of 47 patients with emphasis on its relationship to mitral insufficiency. Circulation 30:759, 1964.
6. Arosemena, E., Moller, J. H., and Edwards, J. E.: Scarring of the papillary muscles in left ventricular hypertrophy. Am. Heart J. 74:446, 1967.
7. Moller, J. H., Nakib, A., and Edwards, J. E.: Infarction of papillary muscles and mitral insufficiency associated with congenital aortic stenosis. Circulation 34:87, 1966.
8. Massumi, R. A., Rios, J. C., Gooch, A. S., Nutter, D., DeVita, V. T., and Datlow, D. W.: Primary myocardial disease. Report of fifty cases and review of the subject. Circulation 31:19, 1965.
9. Harvey, W. P., Segal, J. P., and Gurel, T.: The clinical spectrum of primary myocardial disease. Progr. Cardiovas. Dis. 7:17, 1964.
10. Saphire, A.: Myocarditis. A general review with

an analysis of t hundred nd forty cases, Arch Path. 32:1000, 1941 33:88, 1942.

11 Fowler N. O Gueron, M and Rowlands, D J Primary myocardial disease Circulation 23:498, 1961

12 Die, C. L., Rosenbaum, D Low J C., Blake, R. H and Genovese P D Primary myocardial disease. I—Clinical features, Ann Int. Med. 58:426 1963.

13 Brigden, W : Uncommon myocardial diseases. The non coronary cardiomyopathies Lancet 2:1179 1243, 1957

14 Marriott, H. J L. Electrocardiographic abnormalities, conductive disorders and arrhythmias in primary myocardial disease Progr Cardiovasc Dis 7:99 1964

15 Spodick, D M and Littman, D Idiopathic myocardial hypertrophy Am J Cardiol 1:610, 1958.

16 Barritt D W and Majeed Al Shammaa Heart failure from unexplained cardiomyopathy Brit Heart J 28:674, 1966.

17 Perloff J K Roberts, W C de Leon, A C and O Doherty D The distinctive electrocardiogram of Duchenne progressive muscular dystrophy Am. J Med 42:179 1967

18 Scott, T M and McKeown, C F Sarcoidosis involving the heart. Arch. Path 46:289 1948.

19 Wood, P Chronic constrictive pericarditis, Am J Cardiol 18 1961

Review

Hereditary cardiomyopathy: A new disease model

F I I D I h D
I I

The i r currenc a I r f i s ocardial degener n I t ronary artery i + cor pul monale h n e it il heart disease i s llem io the h i lai I ic t dist The etiol s f thi broad grou f I s rs of cardiac us le u u i hiomyopathies rem n u i m jority of ases f I s m and con gesti e h r i s mon find ngs I n t I t s f cardio- my path es t ll s f tory since som of th r I i t m that are listed as sep r t t t present may turn out to be mer I ffer nt stages of the same disease pr s

The successful sel tive breeding of a strain of Syrian ham ter with a hereditary cardiomyopathy h fered unique op-portunities for in estig t ve cardiology [1-4] This spontaneous lise se is haracterized by the occurrence of focal myocardial

the hamster resembles certain nonvascular myocardial diseases of man in addition the edematous animals respond to therapy with digitalis, diuretics and salt restric tion in the same way as do human patients with congestive cardiac failure.[6,7] Therefore the possibility exists that investigations in the cardiomyopathic hamster will help to clarify the genesis of human cardiomyopathies with similar if not identical lesions.

The following description of some characteristics and the histogenesis of the spontaneous cardiac disease of the hamster is based on studies performed between October 1964 and January 1968, in over 6,500 animals of the BIO 14 6 cardiomyopathic line ranging from 18 to 479 days of age The review of data regarding the behavior and certain specific details of the hamster disease serves to provide an insight into the wide variety of basic problems that can now be analyzed experimentally in the light of this new disease model

Genetic background incidence clinical course

The cardiomyopathic strain of Syrian golden hamsters, designated "BIO 14 6, was derived from inbred lines of *Mesocricetus auratus* developed by Whitney through brother-sister mating from 1956 on [4] The BIO 14 6 line itself has now been inbred for over 20 generations. The cardiac disease observed in this strain originates from a genetically determined metabolic defect that induces degenerative lesions

From the Bio-Research Institute, Cambridge, Mass
Supported in part by the United States Public Health Service Research Grant Nos HE-09791 AM-08196 and FR 05525 and in part by the Hartford Foundation.

May 1969 Vol. 77 No. 5 pp 686-696

in all striated muscles, and with particular consistency and intensity in the heart. Genetic studies have established a recessive autosomal mode of inheritance of the disease or of the susceptibility to it.[4] It has been established that viral and other infectious agents, as well as nutritional factors (i.e., vitamin E, selenium, thiamine, potassium, and magnesium deficiencies) do not participate in its etiology.

Myocardial degeneration occurs in all animals of both sexes within this inbred line. New cardiomyopathic sublines can be developed through cross-breeding hamsters of a healthy strain with those of the BIO 14.6 strain; a 100 per cent incidence of the spontaneous myocardial pathology may be reached at the third generation (Fig. 1). Progressive, chronic congestive cardiac failure appears to be the ultimate cause of death in more than 90 per cent of the cardiomyopathic hamsters.[4] Nevertheless, the time of onset and the progression of generalized venous congestion are significantly influenced by several environmental (e.g., seasonal housing, dietary) factors and also by other variables, such as the intensity of secondary calcification of degenerating myocardial areas, for example. As judged by histologic studies of cardiac and skeletal muscles, the vigor of the genetic disease of the BIO 14.6 strain has remained unchanged during the past two years. However, a comparison of the mortality rates between 1965 and 1967 in two random samples of 500 animals indicates that the life-span of the cardiomyopathic hamsters has increased from an average of 146 days to 187 days. In 1965, a large percentage of the hamsters died before reaching 150 days of age and very few lived for longer than 250 days; in our present population, some of the animals are 400 days old. This increase in life expectancy reflects a slower progression of congestive heart failure, the reason for which is at present unknown.

With the exception of a few cases in

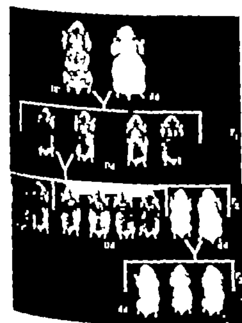


Fig. 1. Cardiac disease that occurs i BIO 14.6 strain of hamsters is transmitted by   autosomal recessive ... and, hence, new cardiom opathic sublines may be developed by cross-breed ng between healthy (DD) and diseased (dd) strains. The carriers (Dd) in the F and F generations do ot show an of the disease manifestations. I the F generation, 100 per cent incidence of cardiom opathy is reached. There is no link bet een the inheritance of the disease and the color of the coat; only white cardiomyopathic hamsters ere selected for the purpose of the present photograph.



Fig. 2. Cardiomyopathic hamsters show normal physical ppearance before generalized edema be comes pparen. Comparison of 2 138-day-old female hamsters, one ithout ppreciable edema (left), the other highly edematous (right), also indicates the variability that occurs in the progression of the spontaneous cardiac condit Fl id accum lation gave rise to a difference eights amounting to 71 grams.

which the disease runs a fulminating course leading to early death, the physical appearance and behavior of the cardiomyopathic hamsters remain normal for a long period despite the presence of heart muscle degeneration. Only when generalized subcutaneous edema is manifest does the presence of the disease become apparent (Fig. [illegible]); thus, there is no characteristic gross symptom [illegible] during the advanced stages of the cardiac condition. In the terminal stage the animals exhibit hyperpnea and cyanosis. Death usually occurs a few weeks after these signs are noted.

As was to be expected, electrocardiogram (ECG) studies showed that the focal myocardial lesions produce alterations in the pathways of cardiac excitation that can be detected in the hamster by surface recordings if appropriate high frequency high gain instrumentation is used. Subsequent histologic examination of the hearts of animals presenting distinct high frequency alterations (notches) within the QRS complex also revealed the presence of myocardial degeneration. Moreover, analysis of the relationship of the surface ECG to focal heart muscle lesions has indicated that variation in the spatial QRS vector magnitude and orientation occurred only in association with fairly extensive myocardial degeneration. ECG changes did not precede the histologically detectable structural alterations. Furthermore, although no correlation was seen between the ECG changes and the severity of the heart muscle disease, the occasional depression or elevation of the S-T segment was not among the early findings. Since this type of focal disease often involves the elements of the conducting system, further correlative ECG and morphologic studies are awaited with interest.

Gross pathology

In hamsters of the cardiomyopathic strain the autopsy findings depend largely if not exclusively on the duration and extent of the congestive cardiac failure. Significant pathologic alterations are not usually grossly detectable during the early stages of the disease since the myocardial lesions are rarely visible by inspection of fresh preparations. Only in cases where secondary calcification of the degenerating foci develops are the heart muscle lesions clearly discernible with the naked eye, appearing as white streaks that follow the direction of the myocardial fibers. With the exception of a few animals with membranous interventricular septal defect no congenital cardiac malformations have been detected.

At the time when gross signs of generalized venous congestion (such as liver enlargement and fluid accumulation) become apparent, there is an appreciable increase in volume and weight of the heart, both ventricles and auricles being affected by varying degrees of dilatation and hypertrophy. During this phase of the cardiac condition there is an increase of the total ventricular mass, ranging between 30 and 80 per cent. Furthermore, analysis of the ratio of left to right ventricular weights indicates that bilateral hypertrophy is present in the majority of animals, predominantly left sided or right sided hypertrophies being less common. In a few cases the upper third of the free walls of both ventricles and the interventricular septum were markedly hypertrophied resembling the lesions of human muscular subaortic stenosis. During the terminal stage of heart involvement when hypertrophy is no longer evident, auricular and ventricular mural thrombi are frequently seen in the greatly dilated flabby hearts (Fig. 3).

The hamsters with an advanced degree of cardiac enlargement exhibit variable amounts of subcutaneous edema, ascites, hydrothorax and often hydropericardium. The liver is invariably enlarged and firm, and its capsule appears to be tense and thickened. In fact, this organ exhibits all the characteristic gross pathologic changes of chronic passive venous congestion. Moderate enlargement of the kidneys as well as congestion of other visceral organs (spleen, pancreas, intestines) are also obvious in hamsters with prolonged cardiac failure. Pulmonary edema of the acute or subacute type not accompanied by any significant liver enlargement or peripheral edema was seen in animals that died before reaching their hundredth day of age, i.e., in animals showing a rapidly fulminating course of the cardiac disease. Ventricular



Fig 3 Organized mural thrombus accompanied by formation of aneurysm in the left ventricle of a stained heart of a 245-day-old cardiomyopathic hamster (Hematoxylin and eosin ×8)



Fig 4 I lesions without secondary calcification in the subepicardial and middle third of the free wall of left ventricle 76-day-old male cardiomyopathic hamster Hematoxylin and eosin ×40

aneurysms and cardiac rupture with hemothorax are noted only during the advanced stages of the more common slowly progressive variety of this cardiac condition.

Histopathology

The first histologically detectable heart muscle lesions appear around the thirtieth day of age in the females and about 10 days later in the males Around the seventieth to eightieth days of age the structurally severed areas show a widespread distribution throughout the heart by this time, the severity of the myocardial disease is comparatively uniform in all animals of both sexes In older hamsters newly formed myocardial lesions are rarely formed and the older foci of degeneration are usually in various stages of healing by connective tissue replacement.[11] Thus, this form of hereditary myocardial degeneration progressive for only about 30 to 40 days following its onset. Although the heart muscle lesions remain focal in nature during the entire course of the pathologic process their localization may show a considerable variation from animal to animal in some hearts the outer two-thirds of the free walls of both ventricles are affected while the subendocardial musculature is more or less spared (Fig 4) in others the subendocardial regions are the sites of predilection for degeneration (Fig 5) The reasons for such qualitative differences in the cardiac disorder are unknown as are their consequences with respect to the clinical course

The myocardial lesions consist of focal myolysis by primary dissolution of myofibrils in the absence of any significant cellular infiltration (Fig 6) In fact, the initially affected areas in the hamster heart closely resemble the condition usually referred to by pathologists as spotty myocytolysis[11] because it is characterized by the disappearance of muscle fiber segments leaving behind sarcolemmal remnants and free muscle nuclei In advanced cases lesions of various sizes and in d



Fig 5 Predominantly subendocardial localization of ... calcified lesions in heart of 74-day-old male ... cardiomyopathic hamster (von Kóssa and hematoxylin and eosin ×10.)

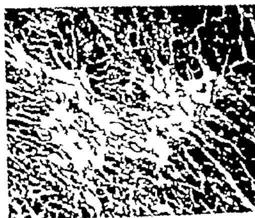


Fig 6 Morphologic characteristics of focal myoly... in the heart of a 50-day-old male BIO 14.6 hamst... Myocardial degeneration proceeds in the absen... of cellular invasion sarcolemmal remnants a... free muscle nuclei are left behind by the disappea... ing muscle fibers. (Hematoxylin and eosin ×45...

ferent stages of evolution and healing are seen some foci show increased vascularization histiocytic proliferation and fibroplasia, while others exhibit calcification and/or progressive sclerosis. Sometimes, and quite unpredictably all lesions may become intensively calcified in a given heart while in another otherwise comparable case such secondary mineralization is completely absent, the findings in the majority of hamsters falling somewhere between these 2 extremes.

The myocardial disease occurs without any morphologic evidence of vascular lesions. In advanced stages, there is dilatation of the cardiac veins and the occasional rupture of capillary-sized vessels results in interstitial hemorrhages especially within or around degenerating areas Similarly valvular lesions are seen only in cases with long-standing cardiac failure, when the intimal layer of the auricles and valves may become markedly edematous and inflamed [4,12]

A reconstruction by the gross and histopathologic observations of the evoluti... of the chronic cardiac conditions in t... hamster permits the recognition of thr... well-defined stages (Fig 7) The fi... stage begins between the twenty fifth a... forty fifth days of age and is characteriz... by the occurrence of focal myocard... lesions. During the second stage (beginni... approximately between the thirty-fi... and fiftieth day) progressive myocard... degeneration takes place fresh lesi... appear in large numbers, while the ol... foci are already in various stages of he... ing The heart muscle disease is the m... severe in this stage when hypertrop... prevails over dilatation in the enlarg... hearts. During the third stage which u... ally begins after the eightieth day of a... the hypertrophy becomes gradually l... obvious because of the extended dilatat... of the cardiac chambers. Concurrent... the extent and severity of the periphe... manifestations of cardiac failure incre... further (Fig 8) The progression of t... terminal stage is rather variable and m... result in death anywhere between ... ninetieth and four hundred and twenti... days of age. Data collected from a la... number of cardiomyopathic hamst... clearly revealed that the extent of hea... damage that can be detected during ... third stage of the disease is not indicat... of the severity of myocardial degenerat...



Fig. 7. In the cardiomyopathic strain of hamsters heart failure develops hr ugh 3 dis nct ages. A During the first stage focal myocardial lesions occur. B During the second stage ompensat r phenomena, hypertrophy and dilatation, begin to take place. C During he third tag he h pertr ph is eplaced by ex nded dilatation. Hearts in photographs are from 62 85 nd 105-da -old male cardiom opathic hamster (Formalin fix and eosin. X10.)



Fig. 8. Progression of arious m fest t ons of ar iac dec mpens ion illustr ted in 3 BIO 14.6 hamsters of the same age (117 da) but in differen stages of the hron ardiac ondition. A Early stage of linical heart failure. Slightly enlarged heart (4 1 mg) and detectable li er congestion (2,875 mg). B More advanced stage of ongesti heart f l re. M der enlargement of heart (578 mg) nd liver (5 100 mg), slight pulmonary congestion. C Terminal stage of cardiocirculat ry insufficiency. Marked cardiac enlargemen (146 mg.), severe liver ongestion (7,135 mg) h drothorax and subcutaneous edema.

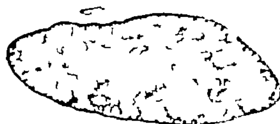


Fig. 9 Massive destruction of hepatic parenchyma by passive venous congestion. Only small islets of viable liver cells are observed in 218-day-old hamster at the terminal stage of progressive cardiac failure. (Hematoxylin and eosin. ×8.)

prevailed at the second stage. This finding points to the possible pathogenic significance of minimal areas of fibrosis and scars seen so often at autopsy in hearts of patients with congestive heart failure of obscure etiology.

In histologic sections congestive changes of varying severity are regularly seen in the liver, spleen, lungs, kidneys, and other visceral organs. With the exception of those occurring in the heart and skeletal muscles, all the gross and histopathologic abnormalities observed in cardiomyopathic hamsters are consistent with long-standing passive venous congestion. Since the histogenesis of skeletal muscle lesions was dealt with in several earlier papers, it is merely noted here that, on the one hand, the involvement of respiratory muscles may accelerate the onset or contribute to the progression of cardiocirculatory insufficiency and, on the other hand, that the course of skeletal muscle disease is significantly influenced by the consequences of failing circulation. The liver appears to be the most severely affected by venous congestion: over three fourths of its cells may become destroyed (Fig. 9). In the edematous pulmonary tissues hemosiderin-laden macrophages ("heart failure cells") appear in large numbers. The progressive atrophy of the inner zone of the adrenal cortex is accompanied by marked hypertrophy of the zona glomerulosa. The last mentioned finding, together with an increased juxtaglomerular index, suggests that stimulation of the renin-angiotensin-aldosterone system occurs during the development of heart failure in this species.[1]

Pathogenesis and miscellaneous observations

Investigations performed so far in hamsters of the cardiomyopathic strain were designed to (1) disclose the primary metabolic defect responsible for muscle degeneration, (2) establish whether the occurrence of myocardial lesions is solely responsible for the subsequent development of congestive cardiac failure, and (3) observe the behavior of the hamster disease under the influence of common cardioactive compounds, changed dietary conditions, and other environmental variables in order to collect data concerning similarities to, and differences from, other pertinent cardiac conditions of animals and man.

Nothing definite is known as yet with respect to the onset and nature of any genetically determined molecular defect that could be confidently assumed to be responsible for muscle degeneration. The possibility that an aberration in the major energy sources of the contractile process is the primary etiologic factor was suggested by observations showing uncoupling of oxidative phosphorylation in both the cardiac[19] and skeletal[20] muscles. It was emphasized that this defective oxidative phosphorylation appears to represent a specific rather than a generalized biochemical abnormality, since it occurred only in striated muscles, where the degenerative lesions actually develop. Interestingly, changes in the adenosine triphosphate, adenosine diphosphate, adenosine monophosphate, and phosphocreatine content of the muscle could not be established in the same experiments. Nevertheless, a significant increase of inorganic phosphate concentration was detected. Furthermore, although it was claimed that, like the serum enzyme changes,[21] a defective sarcosomal oxidative phosphorylation is already present during the early stages of the hereditary disease,[22] data of other investigators are at variance with the last mentioned finding.[23] Thus, whether an impairment of the energy transformation mechanism plays any important role in the onset of the myocardial disease remains open to question.

A reduction in the activity of certain oxidative enzymes (cytochrome oxidase

and succinic dehydrogenase) was demonstrated histochemically in the heart muscle of cardiomyopathic hamsters.[4] However these changes were merely considered as being secondary to degeneration since the decline in enzyme activities was restricted to structurally severed muscle fibers. Additional findings include increased glycolysis and glycogen synthesis[24] as well as enhanced oxidative metabolism as judged by the rate of palmitate-1-^{14}C incorporation into cardiac lipids.[25] Therefore, the working hypothesis that some sort of metabolic anoxia plays an important role in the genesis of myocardial degeneration[12] deserves further exploration.

It should be kept in mind that all biochemical studies summarized above were performed in more or less extensively injured and probably already failing hearts and it is difficult to distinguish between primary and secondary metabolic alterations under such conditions. The only prenecrotic change so far detected in the heart muscle consists of an abnormally enhanced accumulation of intracellular lipid droplets. This increase in myocardial lipid content appears to be independent of the amount or type of fats and carbohydrates ingested and histochemical observations revealed that the diffuse lipid accumulation present throughout the heart of the diseased hamster strain differs from the so-called fatty infiltration in that the former disappears within and around the focal areas of degeneration. An exact interpretation of even this finding is hindered by metabolic adaptive phenomena likely to occur in the cardiomyopathic hamster during the gradual adaptation of heart muscle to the necrotizing genetic defect.[11] As yet the nature of such phenomena is unknown.

We are equally ignorant of the underlying mechanism of cardiac failure that develops in these animals. A definite reduction in work performance of the isolated beating heart of cardiomyopathic hamsters was demonstrated by comparative studies using control [illegible] from a healthy strain. Peak height of contraction, tension time index, tension time per minute and heart rate were significantly lower in the diseased hearts. The progressive myocardial fiber lengthening in response to applied stretching forces was consistently less in the cardiomyopathic strain.[26] The depressed mechanical performance could not be related directly to altered substrate metabolism or to reduction of total muscle mass. It was therefore suggested that a reduction in heart rate and a relative inability of myocardial fibers to lengthen are probably both responsible for the decreased work capacity of cardiomyopathic hamster hearts. Since it may be reasonably assumed that varying degrees of dilatation were already present in the diseased hearts used in these studies, the reduced distensibility of myocardial fibers does not require further explanation.

Analysis of the relationship between myocardial disease and the development of congestive cardiac failure formed the subject of another series of experiments. The injection of catecholamines during the early stage of the genetic disease and the maintenance of young cardiomyopathic hamsters on a low potassium or a low magnesium diet accelerated the onset and enhanced the progression of both the spontaneous myocardial lesions and the development of congestive heart failure.[7] However it was more surprising to obtain data suggesting that the speed and qualitative aspects of healing of the focal myocardial lesions are of more immediate importance than is the extent of heart muscle degeneration as regards the occurrence of overt cardiac failure.[28] A number of factors were observed to selectively influence the healing of focal myocardial lesions without affecting the underlying primary disease, that is, the muscle degeneration itself. For example, agents capable of stimulating protein synthesis (growth hormone, testosterone, insulin and certain potassium salts) were shown to enhance the rate of repair by connective tissue of cardiac lesions,[28-27] while other conditions (inadequate protein nutrition, secondary calcification of necrotic myocardial areas, treatment with actinomycin) interfered with the normal healing processes.[28] In subsequent experiments, the long term consequence of altered healing patterns was studied. Accelerated healing of cardiac damage afforded a beneficial [illegible]tion on congestive heart failure, even completely preventing its development,

some instances interference with reparative processes exerted a clear-cut adverse effect in this respect.[25,27]

Qualitative changes in normal healing patterns were shown to be of equal significance. During a rapid evolution of hypertrophy and/or dilatation there occurs a collapse of structurally preserved myocardial fibers into the areas of degeneration. At this stage the small focal lesions can no longer be recognized by routine histologic studies since fibrosis and scar formation do not take place. This form of healing, i.e. the resulting alterations in the structural architecture of the affected heart, appears to be disadvantageous from a functional point of view.[28] Rapid development of cardiac enlargement, unlike the spontaneous myocardial degeneration itself, can be prevented by the establishment of parabiotic union between a young cardiomyopathic and a healthy hamster. If maintained during a critical phase of cardiac disease (i.e. between about the fiftieth and ninetieth days of age when the majority of myocardial lesions appear and also the healing is most active), the assisted circulation so provided completely prevents the development of congestive heart failure. Once achieved, the protection is not abolished by surgical separation of the parabionts.[12,24] Although the nature of this long-lasting preventive effect is not fully understood, a more efficient healing of heart muscle damage likely plays an important role in this respect. The formation of aneurysms in and an external rupture of the ventricular wall also proved to be connected with altered repair: both phenomena occurred most frequently around diffusely and intensively calcified focal lesions that were surrounded by dense granulomatous tissues.[4]

Since the role of the adrenal cortex in the development of edema of congestive heart failure as well as the sequence and significance of the decrease of cardiac catecholamine stores in the failing heart are much-debated problems, some pertinent data obtained in cardiomyopathic hamsters deserve mention. Although a marked stimulation of the renin-angiotensin-aldosterone system was evidenced by histologic studies,[4] experiments in adrenalectomized hamsters excluded any possible primary importance of aldosterone in the pathogenesis of generalized cardiac edema in this species. In hamsters adrenalectomized at an early stage of their disease and then treated with maintenance doses of either triamcinolone or aldosterone, the degree of edema and of other manifestations of passive venous congestion was the same. However, when animals already in advanced heart failure were adrenalectomized, a more severe progression of fluid retention resulted from substitution therapy with the mineralocorticoid than with the glucocorticoid, indicating an increased sensitivity to the edema-promoting action of aldosterone.[22]

Up to 3 months of age significant differences in cardiac norepinephrine concentrations between cardiomyopathic and control hamsters could not be demonstrated by spectrofluorometric analysis. However, 4-month-old diseased animals with overt signs of heart failure had a markedly lower (−72 per cent) cardiac norepinephrine content than the healthy controls. This decrease in catecholamine stores appeared to follow rather than precede heart failure. Histochemical observations revealed a decline in the intraneuronal concentration of norepinephrine; focal destruction of neural elements was seen only occasionally and only in the terminal stage of the chronic cardiac condition.[29]

Finally, it is noted that treatment with digitalis in hamsters with full-blown cardiac failure exerts a dramatic beneficial effect and prolongs life, at least to a certain extent. However, initiation of prophylactic digitalization during the early stages of the hereditary cardiac disease markedly enhanced the development of myocardial degeneration and thus elicited a rapidly fatal heart failure. This adverse action of normally nontoxic doses of digitoxin could be abolished by concurrent administration of potassium and/or magnesium salts.[7]

Comments

The establishment of an easily reproducible disease model of congestive failure has long been among the basic tasks of research. Surgical and other techniques (e.g. exposure to high altitude, injection

of tin glass balls into the pulmonary and/or coronary vessels) proved to be more or less effective in large animals. However it was soon recognized that rodents with experimentally induced massive myocardial lesions survive for long periods and only occasionally develop congestive heart failure.[81,48]

The observations described and reviewed in the present report appear to indicate that the hereditary cardiomyopathy that regularly occurs in hamsters of the BIO 14.6 strain represents a new and unique disease model with novel perspectives for investigative cardiology. It is especially noteworthy that simply by maintaining appropriate breeder colonies, the cardiomyopathic hamsters can be produced in large numbers for studying spontaneous, focal myocardial degeneration, for investigating the relationships between the myocardial disease and the development of congestive heart failure, for analyzing the genesis of the various manifestations of generalized venous congestion of cardiac origin, for serial testing of new cardioactive compounds or prophylactic measures, and so on. For example, treatments applied between the thirtieth and sixtieth days of age can be evaluated with respect to their influence upon the progression of myocardial degeneration and/or the early phases of healing processes. Furthermore the long-term effects of such periodic treatments can be studied in relation to the evolution of congestive heart failure and even the little-clarified questions relating to the reversibility of peripheral consequences of cardiac decompensation can be approached experimentally.

The chronic cardiac disease of the hamster presents all the known features of congestive cardiac failure. This disease would probably most closely resemble certain degenerative nonvascular heart muscle disorders of man and those progressive cardiac conditions that develop in association with primary muscle diseases (e.g., muscular dystrophies). The late manifestations of the hamster disease can appear to be comparable to the long-term consequences of repeated myocardial infarctions and of many other clinical heart diseases. Nevertheless, it should be kept in mind that, since the fundamental cause of heart failure in man is not known one cannot be certain that it is reproduced by Nature in the hamster disease.

Summary

Focal myocardial degeneration occurs spontaneously in all members of an inbred strain of Syrian hamsters (BIO 14.6 line). The underlying metabolic defect is transmitted by an autosomal recessive gene. The progressive chronic cardiac condition results in the appearance of all the known features of congestive heart failure. Cardiomyopathic hamsters can be produced in large numbers simply by maintaining appropriate colonies through brother-sister matings. The histogenesis and some additional characteristics of this hereditary disease model have been clarified. These and other observations suggest that hamsters of the cardiomyopathic strain offer unique opportunities for investigative cardiology.

REFERENCES

1. Mattingly, T. W.: Changing concept of myocardial diseases, J. A. M. A. 191:33, 1965.
2. Massumi, R. A., Rios, J. C., Gooch, A. S., et al.: Primary myocardial disease: report of fifty cases and review of the subject, Circulation 31:19, 1965.
3. Bajusz, E., and Homburger, F.: Cardiomyopathies, Science 156:1649, 1967.
4. Burch, G. E., et al.: Primary myocardial disease (heart muscle disease, cardiomyopathy). In Andrus, E. C., and Maxwell, C. H., editors: The heart and circulation. Second National Conference on cardiovascular diseases, Washington, D. C., 1965, Federation of American Societies for Experimental Biology, vol. 1, p. 488.
5. Homburger, F., Baker, J. R., Nixon, C. W., and Whitney, R.: Primary generalized polymyopathy and cardiac necrosis in an inbred line of Syrian hamsters, M. Exper. 6:339, 1962.
6. Bajusz, E., et al.: The heart muscle in muscular dystrophy with special reference to involvement of the cardiovascular system in the hereditary myopathy of the hamster, Ann. New York Acad. Sc. 138:213, 1966.
7. Bajusz, E., et al.: Dissociation of factors influencing myocardial degeneration and generalized cardiocirculatory failure, Ann. New York Acad. Sc. In press.
8. Homburger, F., et al.: Hereditary myopathy in the Syrian hamster: Studies on pathogenesis, Ann. New York Acad. Sc. 138:14, 1966.
9. Bajusz, E., and Baker, J. R.: Dystrophic calcification of myocardium as conditioning factor in genesis of congestive heart failure, Proc. Soc. Exper. Biol. & Med. In press.

10. Angelakos, E. T. and B. J. ... unpublished observations.
11. Bajusz, E.: ... per ... subaortic stenosis (hypertrophic obstructive cardiomyopathy) read before the 16th Annual Session of American College of Cardiology, Washington, D. C., ... 1967. Am. J. Cardiol. 19:117, 1967 ...
12. Bajusz, E. ... hereditary myocardial degeneration ... heart failure ... New York ...
13. Schlesinger, M. J. and R... cytology of the heart ... 31:443, 1955.
14. Homburger, ... B. ... R. ... C. W. and W... disease of Syrian hamster ... generalized polymyopathy ... Arch. ... Med. 110:660, 196...
15. Homburger, ... B. ... R. ... C. W. ... the ... lesion of ... muscle ... golden hamster ... 89:133, 1965.
16. Homburger, ... B. ... R. W. ... hereditary ... myopathy ... cardiopathy ... Arch. Path. 81:301, 1966.
17. C... observations ... muscle ... New York ... 138:151, 1966.
18. C... M. ... B. ... Adrenal ... and ... spontaneous hereditary ... heart failure. Fed. Proc. 27:..., 1968.
19. Opie, L. H. ... B. ... A. J. ... Oxidative ... hereditary myocardiopathy ... 2:1213, 1964.
20. Lochner, A. ... Oxidative phosphorylation ... the hereditary muscle ... of the Syrian hamster. Clin. Sc. 33:409, 1967.
21. Eppenberger, M. ... C. W. Baker, J. R. ... Serum phosphocreatine kinase ... hereditary ... and cardiac necrosis ... golden hamster. Proc. Soc. Exper. Biol. & Med. 117:465, 1964.
22. Wrogemann, K. and Blanchaer, M. C.: Respiration and oxidative phosphorylation by muscle and heart mitochondria of hamsters with hereditary myocardiopathy and polymyopathy. Canad. J. Biochem. 46:323, 1968.
23. Blink, A. J. and Lochner, A.: Work performance of the isolated perfused beating heart in the hereditary myocardiopathy of the Syrian hamster. Circulation Res. 21:391, 1967.
24. Bajusz, E.: Participation of endocrines in the metabolic adaptation of heart muscle to a genetic defect, read before the 24th International Congress of Physiological Sciences, Washington, D. C., Aug. 25 to 31, 1968.
25. Bajusz, E.: Interrelationships between reparative processes in myocardium and the development of congestive heart failure. Rev. Canad. Biol. 27:15, 1968.
26. Bajusz, E.: Influencing the healing of spontaneous hereditary myocardial necrosis, read before the 6th Latin American Congress of Pathology and the 1st Panamerican Meeting of the International Academy of Pathology, San Juan, Puerto Rico, Dec. 10 to 17, 1967 (abstr.).
27. Bajusz, E.: Stimulation of healing of spontaneous myocardial lesions by anabolic hormones and its effect upon the development of congestive heart failure. Cardiovas. Res. In press.
28. Bajusz, E., Baker, J. R., and Nixon, C. W.: Prevention of congestive heart failure by paralyzers, read before the 51st Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, Ill., April 16 to 21, 1967. Fed. Proc. 26:407, 1967 (abstr.).
29. Bajusz, E.: The role of the adrenal cortex in the pathogenesis of spontaneous, hereditary congestive heart failure. *In* Jasmin, G., editor: Endocrine aspects of disease processes, St. Louis, 1968, Warren H. Green Publishing, Inc.
30. Angelakos, E. T., King, M. P. and Bajusz, E.: Cardiac catecholamine stores in a strain of hamsters developing spontaneous heart failure, read before the National Meeting of the American Federation for Clinical Research, Atlantic City, April 30, 1967. Clin. Res. 15:195, 1967 (abstr.).
31. Bajusz, E.: Conditioning factors for cardiac necroses, New York, 1963, Intercontinental Medical Book Company, pp. 261-271.
32. Bajusz, E.: Experimental pathology and histochemistry of heart muscle. *In* Bajusz, E., and Jasmin, G., editors: Methods and achievement in experimental pathology, Chicago, 1967, Year Book Medical Publishers, Inc., vol. 2, pp. 172-233.

Bedside transvenous cardiac pacing

Alan S Rosenberg M.D
James I Grossman M.D
Doris J W Escher M.D
*Seymour Furman M.D***
Bronx N Y

Permanent and temporary transvenous endocardial pacing has become widely accepted since the initial clinical report in 1959[1] It is effective in complete heart block with Adams-Stokes seizures[2] or congestive heart failure, in marked bradycardia or complete heart block following acute myocardial infarction [3] and in digitalis-induced arrhythmias with high degrees of atrioventricular (A V) block. It is efficacious in resuscitation after cardiac arrest[4] and for control of ventricular tachyarrhythmias.[7] Many of these problems are therapeutic emergencies with insufficient time for patient transport to medical centers where the majority of pacemaker insertions are performed. Even with suitable facilities, patients must be moved from bed to fluoroscopy unit, which may be hazardous for the acutely ill patient It has been estimated that at least 45 minutes is required for transport of a patient to a fluoroscopy unit assembly of the necessary personnel and insertion of a transvenous electrode with stable pacing

The commonly used pacemaker catheters† may be stiff and perforation of the heart or vessels result from their blind insertion.[8] A soft flexible electrode wire catheter (Flexon steel wire electrode‡) inserted at the bedside without the aid of fluoroscopy[9-11] has obviated this hazard. However published experience with this method of transvenous insertion is limited In our hands the Flexon steel wire was too light and flexible causing difficulty in manipulation and inconsistent pacing This report details our experience with 102 patients using a new Elecath "Semi Floating (S-F)§ transvenous pacemaker catheter for bedside insertion. These results will be compared with 19 cases using the Flexon steel wire electrode.

During an 8 month period 111 patients, ranging in age from 32 to 96 had bedside transvenous pacemaker insertions. The indications for pacing are listed in Table I The miscellaneous group included several

From the Cardiology Service, Division of Medicine, and the Cardiothoracic Service, Division of Surgery Montefiore Hospital and Medical Center East 2 4 St., Bronx, N Y 0467

This study was supported in part by Grant HE 04666-09 United States Public Health Service.

*Cardiology resident.
**Attending Physician, Division of Medicine and Physician in Charge, Cardiac Catheterization Unit. Address requests for reprints to Doris J W Escher, M.D Montefiore Hospital and Medical Center 111 East 210 St Bronx, N Y 10467
***Attending Surgeon, Cardiothoracic Surgical Service.

†U S.C.I. 5630 unipolar or 565 or 5653 bipolar United States Catheter & Instrument Co Glens Falls, N Y
‡Flexon probe unipolar 50. Flexon steel, American Cyanamid Co Danbury Conn.
§Elecath Unipolar "Semi Floating Electrode Electro Catheter Corp., Linden, N. J.

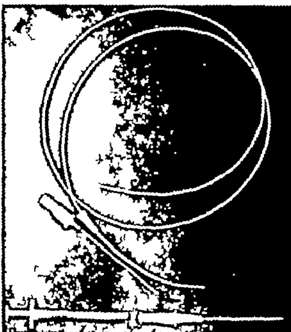


Fig. 1. Below: Bardic ... with attached syringe. Box: Electrode with ... placed through soft portion of ... Below this ... inner cutting core removed from soft part.

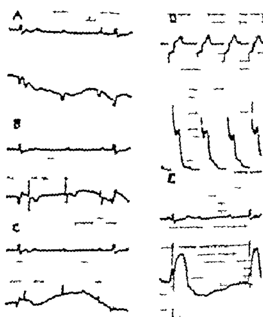


Fig. 2. Simultaneous Lead 2 (upper tracing) and intracardiac (lower tracing) electrogram. Intracardiac recording with Elecath "Semi-Floating" electrode in upper (A), mid (B), and low (C) right atrium. D, Peripheral and right ventricular paced record. E, Peripheral and intraventricular electrogram.

patients with bradycardia alternating with tachycardia and one each with bradycardia associated with hyperkalemia and carcinomatosis. The remaining 10 patients had electrode insertions for arrhythmia diagnosis.

Method

Using sterile technique, an Angiocath (Fig. 1) is inserted percutaneously into the left or right subclavian vein. Although less desirable, a median basilic vein can be used. Following withdrawal of the metal core, a flexible electrode catheter is passed into the vein through the soft Angiocath and advanced to the right ventricle. The catheter position is determined by electrograms with the V lead connected to the intracardiac electrode[1] (Fig. 2). The recording instrument should be powered through a well-grounded outlet. A 45 minute time limit was set from the beginning of the bedside procedure to the achievement of consistent ventricular pacing. When this limit was exceeded, the patient was moved to the fluoroscopy unit where electrode-positioning into the right ventricular apex was accomplished under direct vision.

As soon as an intraventricular complex is recognized (Fig. 2), the electrode is attached to the negative pole of an external pacemaker and a skin electrode (steel plate or insulated subcutaneous steel suture) is connected to the positive pole (Fig. 3). Placement of the electrode is considered optimal when consistent ventricular pacing occurs at a threshold of 1.5 milliamperes or less. The soft Angiocath is then carefully withdrawn from the skin and over the electrode. When feasible, chest x-rays should be obtained after insertion to determine the position of the electrode. In our series, the electrode tip was usually found in the right ventricular apex or low outflow tract (Fig. 4, A and B).

A pacemaker rate of 60 to 70 beats per minute is established with the final current set at two to three times the threshold of cardiac response. Depending upon the clinical conditions, either the demand or fixed-rate mode of pacing may be employed. The catheter electrode and the lead to the skin electrode are fixed in place

Bardic Angiocath, C. R. Bard Inc., Murray Hill, N. J.

Table I *Patients paced using Elecath and Flexon steel electrodes*

Indications for pacing	*Total patients*	*Survivors*	*Average duration of pacing (days)*
High grade heart block	3	37	5
Myocardial infarction with high grade heart block or bradycardia†	4	17	4
Cardiac arrest	14	7	1 8
Permanent pacemaker failure	9	9	2
Digitalis toxicity with high grade block	6	5	3
Miscellaneous	8	6	4 1

Several patients are listed in more than one category
†Twenty-five patients had inferior wall infarctions, 1 with complete block.

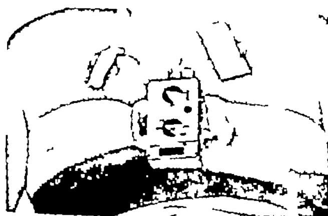


Fig 3 Elecath "Semi-Floating" unipolar electrode in position in left subclavian vein. Indifferent electrode on anterior chest wall below right clavicle. Excess wire coiled and secured by nonallergic tape. The generator is connected to cardiac electrode (cathode) at negative pole

...th strips of nonallergic adhesive tape (Fig. 3). The pulse generator is secured by four strips about the neck and chest. The dressings must be changed several times weekly and topical antibiotics should be applied to the site where the catheter and ground wire enter the skin. Oxacillin 1Gm daily is given while the electrode is in place. When indicated the electrode catheter may be removed or replaced with a permanent transvenous pacemaker catheter. During permanent implantation, the heart rate was maintained with the temporary electrode. Following implantation the temporary electrode should be removed under fluoroscopy to avoid displacement of the permanent catheter. For the first several days, all patients should have continuous bedside electrocardiographic monitoring. When indicated, the monitor may be temporarily disconnected and the patient encouraged to ambulate.

Results

Flexon steel electrode The Flexon steel electrode was used early in the series in 19 patients (Table II). In 5 of 6 patients the electrode was advanced successfully into the right atrium for diagnosis of complex arrhythmias. In 7 of 13 patients right ventricular pacing was successful transiently but only 2 paced for more than two hours. The electrode in one of these patients was found curled in the right atrium at autopsy. In the 6 patients in whom pacing was not accomplished the electrode could not be advanced into the right atrium ... the tricuspid valve in ... ventricular ... entered ... sixth case but ... occ...



Fig. 4. X-ray of Elecath "Semi-Floating" electrode in position in right ventricular outflow tract. Alternate position would be in right ventricular apex. A, Posterior anterior view. B, Right lateral view.

The ventricle was entered in 4 of 7 attempts from the subclavian vein, in 2 of 4 from the median basilic vein, and in 1 of 2 attempts from the external jugular vein. In the 4 cases where the ventricle was entered from the subclavian vein, only intermittent pacing was achieved.

Elecath electrode. One hundred and two Elecath S-F electrodes were inserted transvenously, 63 via the left subclavian vein, 33 via the right subclavian vein, 5 through either median basilic, and 1 through the external jugular. Ninety-eight Elecath S-F electrodes were inserted for pacing, 4 for diagnosis of arrhythmias. As previously noted, transvenous pacing was considered successful if capture of the ventricles occurred in less than 45 minutes from the start of the procedure. By these criteria, Elecath S-F electrode pacing was achieved in 71 of 98 cases (72 per cent) (Table III). The average time needed for the procedure was 18 minutes, with 30 per cent of the patients requiring only 5 minutes or less. In 12 other patients (12 per cent) where bedside positioning was ineffective, pacing was secured within 20 minutes with fluoroscopic aid, but failed in a thirteenth patient. In 9 patients the electrode did not enter the right atrium; in 6 others the Elecath S-F electrode could not be advanced across the tricuspid valve. These 15 patients were treated medically or had fluoroscopically aided femoral vein electrode insertion.[11] Four Elecath S-F electrodes were inserted successfully into the right atrium for diagnosis of complex arrhythmias (Table III).

Sixty nine of 83 patients (83 per cent) were paced with the Elecath S-F electrode for more than 24 hours, and 54 (65 per cent) for more than 3 days (Table IV). One patient was paced for 28 days. Eight patients (10 per cent) were paced for less then 3 hours. Five of these pacing till death died of cardiogenic shock following myocardial infarction. Two others had temporary pacing for less than 2 hours prior to and during scheduled pacemaker implantation. The remaining patient died with ventricular fibrillation 30 minutes after insertion when the skin electrode became disconnected. Eighty of 83 installations (96 per cent) were still functional when the Elecath S-F electrode was removed. The duration of pacing for fluoroscopically positioned catheters was 5 days, not appreciably different from the 4 day average for the total group.

Comparison of electrode insertion time. Either of the two electrodes could be advanced more readily into the right atrium from the subclavian rather than from the median basilic vein. (Mean time from the subclavian vein was 4 minutes for the Elecath S-F electrode and 5 minutes for the Flexon steel electrode. Mean time from the median basilic vein was 24 minutes for

Table II. The Flexon steel electrode in 19 patients

Pacing				Diagnostic			
Success		Failure		Success		Failure	
Insertion site	No. of patients	Insertion site	No. of patients	Insertion site	No. of patients	Insertion site	No. of patients
SCV	4	SCV	3	SCV	3	MBV	1
MBV	2	MBV	2	MBV	2		
EJV	1	EJV	1				
Total	7		6		5		1

Abbreviations: SCV, subclavian vein; MBV, median basilic vein; EJV, external jugular vein.

Table III. Elecath electrode experience in 10 patients

Pacing		Diagnostic	
Success	Failure	Success	Failure
At bedside, 71 After fluoroscopy, 12	15	4	0

Table IV. No. of patients including post fluoroscopy patients who were paced

Type of electrode	Duration of pacing				
	0-3 hours	3-12 hours	12-24 hours	1-3 days	More than 3 days
Elecath	8	5	1	15	54
Flexon steel	5	0	0	1	1

Table V. Electrode mean entry time from subclavian vein puncture

Electrode	Minutes to right atrium	Minutes to right ventricle†
Elecath	4 (93 cases)*	18 (96 cases)
Flexon steel	5 (14 cases)	32 (8 cases)

*Four cases of arrhythmia diagnosis included.
†12 failures or successful cases only after fluoroscopy are counted as 45 minute attempts.

the Elecath S-F electrode and 16 minutes for the Flexon steel electrode.) There was no difference in reaching the right atrium from either left or right subclavian vein (3 to 4 minutes) with the Elecath S-F electrode. The mean entry time of the Flexon steel electrode was comparable to that of the Elecath S-F electrode. The right ventricle was entered after subclavian insertion in 18 minutes using the Elecath S-F electrode and 32 min using the Flexon steel electrode (Table

Complications Twelve of 83 patients (14 per cent) failed to pace consistently Repositioning at the bedside was done easily in almost all cases, requiring only minimal manipulation Malposition occurred most often in the first day or two after insertion usually in patients with a large right ventricle Two of 10 patients in whom the Elecath S-F electrode was positioned fluoroscopically were subsequently repositioned under electrocardiographic control

Local infection at the site of insertion occurred in 3 patients, necessitating removal of the Elecath S-F electrode Infection did not appear to be a problem if local antibiotics were applied to the insertion site The metal tip of the Elecath S-F electrode originally was a silver-soldered platinum tip which occasionally developed a partial black coating It was associated with a slightly elevated threshold but not enough to interfere with pacing Subsequent Elecath S-F electrodes with gold plated tips or crimped non soldered platinum tips have not presented this difficulty

Early in the total series of 106 subclavian vein punctures, ? patients sustained a partial pneumothorax The subclavian artery was entered in another patient Bleeding stopped with five minutes of manual compression There were no instances of catheter perforation of the ventricle or a vessel no instances of bacterial endocarditis catheter clot or pulmonary embolization [3]

Discussion

There are inherent advantages to using a bedside technique for transvenous pacing. Rapid easy insertion without fluoroscopy can be accomplished in patients who need immediate pacing Fluoroscopy essential when stiff wire electrode catheters are employed commonly is unnecessary when soft flexible electrodes are used However excessively flexible electrodes such as the Flexon steel wire cannot be manipulated and in our experience take too long to float to the right ventricle The Elecath S-F electrode, utilized in 98 patients for pacing was soft and flexible enough to make perforation unlikely but sufficiently firm to permit easy advancement and manipulation

It generally took longer for both electrodes to cross the tricuspid valve than to enter the right atrium. Contrary to an earlier report [11] positioning the patient on the left side did not facilitate passage across the tricuspid valve. Recognition of intra-atrial electrocardiographic complexes was of help in locating the electrode tip. At the superior vena cava-right atrial junction the P wave is negative (Fig 2, A) while at the inferior vena cava-right atrial junction the P wave is predominantly positive (Fig 2 C) At the midatrial level the P wave is tall narrow and biphasic (Fig 2 B) When the electrode tip approaches the tricuspid valve the QRS complex usually becomes larger

The superiority of the Elecath S-F electrode was most notable in the stability of pacing Eighty three per cent of successful Elecath S-F electrode insertions paced for more than one day whereas only 28 per cent of successful Flexon steel electrodes paced for this long The advantages of the Elecath S-F electrode prompted its exclusive use after the early stages of this study

The incidence of complete heart block in acute myocardial infarction is about 8 per cent In view of the reported mortality of 40 to 100 per cent in untreated cases,[4,16,17] prompt recognition and treatment is imperative. Seven of 24 patients with myocardial infarction and A V block (29 per cent) died in cardiogenic shock despite pacing with two of the deaths occurring in patients paced with the Flexon steel electrode The 29 per cent mortality rate in our series is similar to previous reports,[2,17] indicating early pacing may reduce mortality

Pacing is indicated when second and/or third degree block is associated with congestive failure, cerebral symptoms, or Adams-Stokes seizures. In 37 such patients, temporary transvenous pacemakers provided a safeguard for the patient while the course of the heart block was assessed prior to permanent implantation High grade heart block, often with Adams-Stokes seizures or congestive failure may result from electrode fracture or pulse generator failure in patients with implanted units. A temporary electrode will sustain the patient until the permanent unit is repaired

Short term pacing may be indicated in digitalis-toxic patients manifesting high grade heart block or in those with block who require suppressive antiarrhythmic agents. Pacing usually employing the demand mode prevents asystole or suppresses escape ventricular arrhythmias. Five of 6 patients with digitalis-induced arrhythmias, 3 receiving quinidine with second degree block, and 4 of 5 with tachyarrhythmias alternating with bradycardia were managed successfully. One death occurred in a digitalis-toxic patient where pacing was a heroic last resort.

Either the right or left subclavian vein proved satisfactory for insertion of pacer catheters. When the median basilic vein was used the time required to reach the right atrium was increased and success less certain. Further with this route of insertion electrode position is affected by movement of the arm and shoulder. Even with immobilization of the extremity intermittent pacing occurs. The external jugular vein also may be used for insertion. This method however usually requires a cutdown on the vein which is time-consuming. The femoral route has had only limited and unsuccessful trial with these electrodes. Subclavian vein puncture when done correctly is a safe and rapid procedure. Only three complications occurred in 106 venipunctures.

The Elecath "Semi Floating" electrode has proven to be sufficiently flexible to obviate fluoroscopy but firm enough for easy manipulation. It permitted stable pacing in 83 of 98 patients (85 per cent) including 71 by bedside insertion in less than 45 minutes (average of 18 min.) and in 1? following fluoroscopic aid. Sustained pacing usually was maintained (average of 3 days) with 14 per cent requiring early accomplished bedside repositioning. Significant complications were small pneumothoraces, and minimal bleeding following subclavian artery puncture. This method appears to be a relatively safe, rapid and effective means of emergency cardiac pacing.

Addendum

Since compilation of this data, additional 100 patients have had subclavian Elecath S-F electrode insertions with similar success pattern. In this group we have had one infection, three arterial punctures readily controlled by brief pressure and no pneumothoraces.

REFERENCES

1. Furman, S. and Robinson, C. The use of an intracardiac pacemaker in the correction of total heart block, S. Forum 9:245, 1959
2. Sowton, E. Cardiac pacemakers and pacing. Mod. Concept. Cardiovas. Dis. 36:31, 1967
3. Mueller, O. and Bellet, S. Treatment of intractable heart failure in the presence of complete atrioventricular heart block by the use of the internal cardiac pacemaker. New England J. Med. 265:768, 1961
4. Paulk, E. A. and Hurst, J. W. Complete heart block in acute myocardial infarction. Am. J. Cardiol. 1:695, 1966.
5. Schwartz, L. S. and Schwartz, S. P. The effects of digitalis bodies on patients with heart block and congestive heart failure. Progr. Cardiovas. Dis. 6:366, 1964
6. Portal, R. W. The emergency treatment of Stokes-Adams attacks by the electrode catheter. Proc. Roy. Soc. Med. 56:281, 1963.
7. Heiman, D. F. and Helwig, J. J. Suppression of ventricular arrhythmias by transvenous intracardiac pacing. J. A. M. A. 195:1150, 1966.
8. Kimball, J. and Killip, T. A simple bedside method for transvenous intracardiac pacing. Am. Heart J. 70:35, 1965
9. Harris, C. Hurlburt, S. Floyd, W. and Orgain, E. Percutaneous technique for cardiac pacing through the subclavian vein. Am. J. Cardiol. 15:48, 1965
10. Mobin-Uddin, K. Smith, P. Lombardo, C. and Jude, J. Percutaneous intracardiac pacing through the subclavian vein. J. Thoracic & Cardiovas. Surg. 54:545, 1967
11. Ba. G. and Silversten, E. Intracardiac pacemaker as emergency treatment in Stokes-Adams attacks, Nord. Med. 76:830, 1966.
12. Kastor, J. A. DeSanctis, R. W. Hawthorne, J. W. and Schwartz, G. H. Transvenous atrial pacing in the treatment of refractory ventricular irritability. A. I. t. Med. 66:939, 1967
13. Kerr Szanto, M. The subclavian vein, a constant and convenient intravenous injection site, Arch. Surg. 72:179, 1956
14. Bertrand, C. Zohman, L. and Williams, M. Intracardiac electrocardiography in man, Am. J. Med. 26:534, 1959
15. Furman, S. Cardiac pacing, Am. Heart J. 70:830, 1965
16. Julian, D. G., Valentine, P. A. and Miller, G. G. Disturbances of rate, rhythm and conduction in acute myocardial infarction, Am. J. Med. 37:915, 1964.
17. Parsonnet, V. Zucker, R., and Gilbert, L. Evaluation of transvenous pacing of the heart in complete heart block following acute myocardial infarction, Israel J. M. Sc. 3:306, 1967
18. Nathan, D. A., Center, S. Pina, R. E., Medow, A., and Keller, W.: Perforation during indwelling catheter pacing, Circulation 3?, 1966

Treatment of "hypertensive encephalopathy" (accelerated hypertension) Part II

Marvin Moser M D
White Plains N Y

A non-diuretic benzothiadiazine drug diazoxide (Hyperstat) has been evaluated over the past 4 to 5 years for the treatment of hypertensive crises. It is not as yet commercially available When given intravenously (250 to 350 mg in 15 to 30 sec.) dramatic lowering of blood pressure usually occurs within 1 to 2 minutes. The duration of the effect is variable (from 1 to 18 hr) Repeated injections frequently do not produce the same degree or duration of blood pressure lowering Diazoxide presumably produces its effect by a direct action on arteriolar smooth muscle since peripheral resistance is lowered and cardiac output does not decrease despite a marked fall in blood pressure. This drug appears to be of great value in treatment where a rapid reduction in blood pressure is indicated (acute pulmonary edema or severe cerebrovascular symptoms)

Diazoxide administration results in the lowering of blood pressure when the patient is in the recumbent position and usually does not produce pronounced postural blood pressure changes. Side effects include transient hyperglycemia and occasional electrocardiographic abnormalities (S-T and T wave changes) suggestive of coronary insufficiency After several injections the patient is usually able to begin oral therapy with other agents. Diazoxide should not be administered on a long term basis or by mouth because of its potential metabolic side effects (hyperglycemia hirsutism and edema)

Veratrum derivatives have little if any place in the treatment of accelerated hypertension Although these drugs may be very effective as antihypertensive agents, their therapeutic and toxic dosage ranges are very close and side effects may be quite severe following their use. Other drugs are easier to administer and generally more effective

Trimethaphan camphorsulfonate (Arfonad) a short-acting ganglion-blocking agent has been advanced by some investigators as the treatment of choice in hypertensive encephalopathy This drug is extremely useful in the treatment of congestive heart failure in patients with hypertensive encephalopathy but because of its extremely short duration of action (5 to 15 min) it should not be considered the agent of choice in the patient who presents without pulmonary edema A continuous infusion must be given and blood pressures must be checked every 10 to 15 min. to avoid a hypotensive reaction Constant blood pressure checking may produce extreme irritation and restlessness in an already agitated patient and large doses of sedatives may have to be given. This greatly delays the time when the patient is able to start oral feedings and oral therapy Longer-acting agents, such as pentolinium or mecamylamine are equally effec

*Physician in-charge of Hypertension Section, Montefiore Hospital and Medical Center New York, N Y and Associate in Clinical Medicine, Albert Einstein College of Medicine, New York, N Y

May 1969 Vol 77 No. 5 pp 704-706

tre, are safe when used properly and do not require the constant monitoring that is necessary when trimethaphan is used

In the presence of pulmonary edema where acute blood pressure lowering for a short period of time is indicated trimethaphan is effective in producing arteriolar and venodilation and venous pooling of blood in the splanchnic and peripheral areas. Its action therefore produces a chemical or medical phlebotomy. In the patient with extremely high diastolic pressures, marked arteriolar constriction and pulmonary edema, it is probably more effective in reducing venous return and increasing cardiac output than the use of peripheral tourniquets. In these cases of severe hypertension it is probably the drug of choice. Trimethaphan is administered slowly in a dosage of 500 mg given in a liter of glucose and water or in a more concentrated solution if fluid restriction is indicated. The drug is administered at .25 to .5 mg. per minute varying dosage with the blood pressure response.

Trimethaphan may also be useful in emergency therapy since it is more readily available than pentolinium which may not be a standard drug in many hospitals. Initial blood pressure lowering can be achieved with trimethaphan while waiting for the longer acting preparations to be obtained

In acute hypertensive crises during surgery where a brief duration of effect is required, the shorter-acting ganglion blocker (trimethaphan) is also useful.

Subcutaneous or intramuscular guanethidine may also be effective in the treatment of hypertensive encephalopathy although experience with it is limited. Apparently the initial pressor response noted after intravenous administration is not observed. There is a rapid blood pressure lowering effect (within 1 to 2 hr) when guanethidine is administered in this manner as contrasted to the 3 to 4 day delay in antihypertensive activity when the drug is given orally Ten to 15 mg are given immediately and the dosage is repeated as necessary to keep blood pressure at acceptable levels Duration of effect is prolonged (from 3 to 24 hr following a single dose)

Sodium nitroprusside has also been advocated in the treatment of "accelerated" hypertension This drug is an effective vasodilator and when administered intravenously has been effective in lowering blood pressure. We have had no experience with this agent and it is not at present available for use in most hospitals

Personal experience with hydralazine (Apresoline) in the treatment of hypertensive encephalopathy has not been entirely satisfactory This drug in doses of between 15 and 40 mg intramuscularly or intravenously every four to six hours, is effective in the treatment of the hypertension associated with acute glomerulonephritis and toxemia of pregnancy and/or eclampsia but it is only occasionally useful when used alone in accelerated hypertension We do not therefore use hydralazine unless the drugs reviewed above are ineffective or not readily available

There are other newer agents that have been advocated for use in the treatment of malignant hypertension but experience with them is limited

Treatment of "accelerated hypertension" and renal insufficiency

The syndrome of malignant or accelerated hypertension and uremia may represent the end stage of chronic glomerulonephritis or pyelonephritis or may reflect the occurrence of malignant nephrosclerosis with fibrinoid necrosis of the small arteries and arterioles as a result of long standing and increasingly severe essential hypertension Regardless of the etiology the immediate treatment of this serious situation is essentially the same, and is extremely difficult.

In the presence of a blood urea nitrogen in excess of 50 to 60 mg per cent and an elevated serum creatinine level there is some danger in lowering the blood pressure since this further decreases the already severely impaired renal blood flow In addition, the benefits of blood pressure control may be limited and may not alter the prognosis in some of these cases.

Despite these objections, there are several valid reasons for attempting blood pressure lowering in these patients. Since the prognosis is extremely poor and death will occur over a three to six period of time or less if they are

there is little to lose by the cautious lowering of blood pressure in these individuals. Treatment is aimed at (1) improvement in symptoms such as visual disturbances, nausea and/or vomiting, congestive heart failure, and encephalopathy; (2) the possible reversal of the severe arteriolar pathology of the malignant phase of hypertension. There is some pathologic evidence that suggests a disappearance of fibrinoid material from the arteries with a change to a more benign form of pathology with intimal fibrosis following blood pressure lowering in these cases. This may not alter the basic pathologic process such as chronic glomerulonephritis if this is present, but may decrease the vascular factor that at least partially contributes to the rapidly progressive renal insufficiency. In patients with renal failure solely on the basis of vascular disease, reversal of necrotizing vasculitis may be even more beneficial.

The same drugs are used in the treatment of accelerated hypertension with uremia as in cases without renal failure. They are, however, used more cautiously and an attempt is made to slowly lower blood pressure only to those levels (150 to 160/100 to 110 mm. Hg) where theoretically at least the edema and fibrinoid changes of the blood vessel wall may have an opportunity to regress. Occasionally, the use of parenteral hydralazine or alpha methyldopa (Aldomet) may be of some theoretic advantage because of their ability to lower blood pressure acutely without seriously decreasing renal blood flow. Experience has indicated that if blood pressure is lowered, some patients will continue on a more benign course for a prolonged period of time.

Summary

1. Patients with accelerated or "malignant" hypertension should be treated vigorously. If emergency treatment is successful and azotemia is not present, long-range prognosis is good.

2. The parenteral drugs of choice are reserpine or pentolinium (Ansolysen). If reserpine is ineffective after several doses, intravenous diazoxide (if available) and intravenous ethacrynic acid should be given.

3. Trimethaphan is the drug of choice in treating the patient with "accelerated" hypertension and pulmonary edema.

4. Oral medication should be started as soon as possible after gastrointestinal symptoms are under control.

5. In patients with accelerated hypertension and azotemia, blood pressure lowering is approached more cautiously, but is indicated in an attempt to reverse the vascular factors that may complicate the underlying renal disease. Prognosis in these cases is guarded even after successful blood pressure reduction.

REFERENCES

1. Byrom, F. B.: The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension, Lancet 2:201, 1954.
2. Simpson, F. O., and Smirk, F. H.: The treatment of malignant hypertension, Am. J. Cardiol. 9:868, 1962.
3. Kincaid-Smith, P., McMichael, J., and Murphy, E. A.: The clinical course and pathology of hypertension with papilledema (malignant hypertension), Quart. J. Med. 21:117, 1952.
4. Freis, E. D.: A method for administering the antihypertensive agents, Arch. Int. Med. 98:444, 1956.
5. Moser, M., and Goldman, A. G.: Hypertensive vascular disease, Philadelphia, 1967, J. B. Lippincott Company.
6. Brest, A. N., and Moyer, J. H.: Therapy of hypertensive emergencies in hypertension: recent advances, Philadelphia, 1961, Lea & Febiger Publishers.
7. Gifford, R. W.: Hypertensive emergencies and their treatment, Med. Clin. North America 45:441, 1961.

Reflex vasodilatation in the treatment of peripheral vascular disease

Organic obstructive arterial disease usually develops [illegible] levels within isolated segments of the peripheral vascular system. Symptoms of ischemia with cutaneous changes in the feet and toes are among the earliest manifestations of significant arteriosclerotic and diabetic peripheral vascular disease. One of the objectives in therapy is to produce dilatation of the arterial and small capillary vessels [illegible] the vicinity of the lesion in an attempt to revascularize the area by opening new blood vessels and enlarging existing ones. Systemic vasodilators are often administered in an attempt to improve peripheral blood flow. Unfortunately the systemic vasodilators which produce widespread peripheral dilatation often result in palpitation, giddiness, hypotension, and syncope. The tone of all vessels of the body [illegible] rather than the tone of only those vessels of the diseased part. Reduction of dosage to a level below that which produces undesirable symptoms frequently means that the blood flow is below the level of clinical efficacy. Furthermore, to increase the blood supply to the second toe by dilating all the vessels of the body or by performing a lumbar ganglionic block before other more physiologic and simple methods are tried seems unnecessarily drastic.

The physician can usually produce a significant degree of local vasodilatation in the digits of the feet and hands by taking advantage of the physiologic principle of reflex vasodilatation. The well-known fact that body warmth produces generalized peripheral vasodilatation in the presence of an intact sympathetic nervous system should be exploited to its fullest. The physician should advise his patient to dress warmly at all times. He should wear loose gloves, woolen socks or stockings, sweaters, long sleeved shirts or blouses and avoid damp shoes and clothing, and avoid becoming even slightly chilled. The patient should be taught to give careful attention to the details of everyday living. He should avoid items which cause reduction in peripheral blood flow and should exploit the physiologic procedures for producing and maintaining a state of sustained reflex peripheral vasodilatation. Only if these methods fail should more drastic methods be considered.

G. E. Burch, M.D.
H. L. Colcolough, M.D.
G. C. Miller, M.D.
Tulane University School of Medicine
New Orleans, La.

The evidence for different types of β-adrenergic receptors*

As the result of a study of the relative potencies of five sympathomimetic amines, Ahlquist[1] concluded that there are two distinct types of adrenergic receptors, these he named α and β receptors. Drugs are now known to block the effects of stimulation of one type of adrenergic receptor but not the other. Stimulation of β-adrenergic receptors results in certain inhibitory responses (e.g., vasodilatation and inhibition of various smooth muscles) and excitation of the myocardium leading to positive inotropic and chronotropic responses. Recent evidence, however, has suggested that subgroups exist within the general β-adrenergic receptor grouping.

Lands and co-workers[2] determined the relative potencies of a series of sympathomimetic amines on fatty acid mobilization (rat), cardiac stimulation (rabbit), bronchodilatation (guinea pig), and vaso-

*Supported by a Senior Research Fellowship from the Canadian Heart Foundation and a grant from the Medical Research Council, Canada.

depression (dog), and calculated correlation coefficients, using the logarithms of these relative potencies. It was found that there was a marked similarity in relative potencies for fatty acid mobilization and for cardiac stimulation (correlation coefficient 0.95) and for bronchodilatation and vasodepression (correlation coefficient 0.96); no other significant correlations were found. On the basis of these results, Lands and associates proposed two types of β receptors: β-1 for lipolysis and cardiac stimulation and β-2 for bronchodilatation and vasodepression.

Furchgott[1] has extensively reviewed the use of blocking agents and of sympathomimetic agents in the differentiation of adrenergic receptors. He estimated the relative potencies of epinephrine (E), norepinephrine (NE), isoproterenol (ISO), and phenylephrine (PE), and the dissociation constant (K_β) for pronethalol for β receptors on isolated preparations which had been pretreated with α-receptor blocking agents and with either cocaine or phenoxybenzamine t prevent the ptake of catecholamines into adrenergic nerve endings. He discovered the following: in rabbit aorta nd guinea pig trachea, β receptors had a K_β value of about 3×10^{-8}M and a potency series ISO > E >> NE > PE; in rabbit atria and in guinea pig tria and duoden m, a K_β of about 7.5×10 M and a potency series ISO > NE > E >> PE; nd in rabbit stomach and duodenum K_β of about 5×10^{-7}M and potency series ISO > NE or ≃ E > PE. On the basis of these results, F rchgott concluded that there appear to be t least t o types of β receptors in each pecies.

Dunlop and Sha ks[3] ha recently described the pharmacology of a new type of β receptor blocking agent, I.C.I. 50172 4-(2-hydroxy-3-isopropylaminopropoxy) acetanalide. I.C.I. 50172 prevented the timulant effects of catecholamines on the myocardium, but did not influence the vasodepressor response to isoproterenol. It was less potent than propranolol in antagonizing epinephrine-induced relaxation of isolated guinea pig tracheal chains. On the basis of these findings, Dunlop and Shanks concluded that I.C.I. 50172 appears to be new type of β-adrenergic blocking agent since it blocked only excitatory responses and not inhibitory responses associated with β-receptor activation.

Levy[4-6] has studied extensively the properties of a group of β-receptor blocking agents which do not antagonize the cardiac excitatory actions of catecholamines. These compounds include N-isopropylmethoxamine which blocks rat uterine β receptors, and butoxamine and dimethyl isopropylmethoxamine which block β receptors in rat uterus and peripheral blood vessels.

The investigations of all these workers have strongly supported the concept that separate subtypes of β-adrenergic receptors exist. However, it is uncertain whether these subtypes reflect differences in chemical composition of receptors, flexible conformational variants, differences in receptor accessibility or the varying influence of surrounding molecules. It would also appear premature to propose any definitive classification of subtypes until more information is available on a greater number of species nd organs.

These findings have an important contribution to make to clinical studies on man. It is no longer precise or descriptive enough to speak of β-adrenergic receptor blockade without specifying hat drug is being employed. For example, propranolol potentiated pressor responds to epinephrine, whereas I.C.I. 50172 did not. The value of I.C.I. 50172 and of other compounds capable of producing a similar selective blockade of cardiac β receptors should be investigated in a number of disease states. It would seem unlikely, for example, that I.C.I. 50172 would produce the pressor responses sometimes found in patients with pheochromocytoma following treatment with propranolol, and thus management of the arrhythmias frequently seen in such patients would be facilitated. I.C.I. 50172 would probably also be of no value in the diagnosis of pheochromocytoma because of its failure to block β receptors in blood vessels. Long-term therapy with propranolol has been shown to produce a significant reduction of blood pressure in hypertensive subjects[17]; however, the mechanism of this effect is still not certain. Since I.C.I. 50172 differs from propranolol in not blocking β receptors in blood vessels and in not possessing local anesthetic properties, it would be interesting to determine the effects of I.C.I. 50172 on the course of hypertension. An advantage of the use of I.C.I. 50172 and drugs with selective cardiac β-blocking properties could be probable reduction in the incidence of reduced ventilatory function in asthmatic patients, reported due to therapy with propranolol.[18]

In conclusion, there is increasing evidence to suggest that subtypes of β-adrenergic receptors exist. A mber of drugs have been produced hich selectively block certain β receptors only. I.C.I. 50172 appears t produce relatively selective blockade of cardiac β receptors. It would seem to offer number of advantages in therapy of cardiac conditions since it would be nlikely to produce reduced ventilatory function in asthmatics or to potentiate pressor responses to catecholamines.

Note added i proof. Very recently the synthesis of a new series of β-adrenergic stimulants has been described.[19] These compounds are not susceptible to metabolism by catechol-o-methyl transferase and are thus long acting. They have considerably greater action on bronchial as compared to cardiac muscle and consequently may prove clinically useful as bronchodilators with minimal cardiac effects. These preliminary studies suggest that agonists, in addition to antagonists, may be developed relatively specific sites of β-receptor action and further evidence for different subtypes.

David M. Paton, M.B. Ch
Department of Pharmacol
University of Alberta Faculty of Medic
Edmonton, Alber
Canad

REFERENCES

1. Ahlquist, R. P.: A study of the adrenotrop receptors, Am. J. Physiol. 153:586, 194
2. Ahlquist, R. P.: Agents which block adrenergi β-receptors, Ann. Rev. Pharmacol. 8:259, 196

3. Lands, A. M. Arnold, A., McA Ull J. I. Ladeua, F. P. and Brown, J. G.: Differentiation of receptor systems activated by sympathomimetic amines, Nature 214:597 1967
4. Furchgott, R. F. The pharmacological differentiation of adrenergic receptors, Ann. New York Acad. Sc. 139:553, 1967
5. Dunlop, D. and Shanks, R. G.: Selective blockade of adrenoceptive beta receptor in the heart, Brit. J. Pharmacol. & Chemotherapy 32:201 1968.
6. Levy B.. Alteration of adrenergic responses by N-isopropylmethoxamine J. Pharmacol. & Exper. Therap. 146 129 1964.
7. Levy B. Adrenergic blocking activity of N-tertiary butylmethoxamine (butoxamine) J. Pharmacol. & Exper. Therap. 151:413, 1966.
8. Levy B.: Dimethyl isopropylmethoxamine: selective beta-receptor blocking agent Brit. J. Pharmacol. & Chemotherapy 27:277 1966.
9. Cavallito, C. J. Some relationships between chemical structure and pharmacological activities, A n. Rev. Pharmacol 8:39 1968.
10. Prichard, B. N. C. and Ross, E. J.: Use of propranolol in conjunction with alpha receptor blocking drugs in phaeochromocytoma, Am. J. Cardiol. 18:394 1966.
11. Paton, D. M. Beta adrenergic receptor blockade in the diagnosis of phaeochromocytoma, AM. HEART J. I. press.
12. Prichard, B. N. C. Hypotension from beta adrenergic blocking drugs, AM. HEART J. 69 716 1965.
13. Stephen, S. A. Unwanted effect of propranolol, Am. J. Cardiol. 18:463 1966
14. Hartley D. Jack D. Lunts L. H. C., and Ritchie, A. C. New class selective stimulants of β-adrenergic receptors, N ture 219:861 1968.
15. Brittain R. T. Farmer J. B. Jack, D. Martin, L. E., nd Simpson W. T. 4-[(t Butylammo) methyl]-4-hydroxy-m-xylene-α α'-diol (AH 3365) A selective β-adrenergic stimulant, N ture 219:862 1968.

The value of squatting in the diagnosis of mild aortic regurgitation

Since squatting was shown to soften the sy tolic murmur of hypertrophic obstructive cardiomyopathy and intensify the murmur of fixed aortic stenosis, mitral incompetence, and pulmonary stenosis, have used this simple bedside technique to aid recognition and diagnosis of other murmurs. In diagnosing various murmurs, squatting proved most valuable in the diagnosis of mild ortic regurgitation Here the diagnosis frequently depends solely on the ability of the examiner to hear the soft blowing early diastolic murmur If the murmur is not heard, the diagnosis is missed, for the associated signs of collapsing pulse and ortic run-off are often absent in the mild case. Great responsibility thus placed on the auscultator and this is especially important in examining proponents for life insurance. The extra mortality rating for mild aortic regurgitation without signs of left ventricular hypertrophy is heavy and the underwriter is entirely dependent on the doctor's uscultatory diagnosis.

Unfortunately the graphic recording of the soft aortic diastolic murmur has been technically most unsatisfactory with phonocardiographic machines in current use. This murmur has very high frequency and low amplitude and its registration requires so much amplification that background noise especially during squatting disturbs the baseline. Without perfect baseline in end-systole and end-diastole any vibrations recorded in early diastole are usually uninterpretable. For these reasons, we have found the ear vastly superior to any graphic recording system available to us. The use of an amplifying stethoscope may have useful place in detecting this type of murmur but have had no experience with this d.

Any maneuver which augments this murmur will be of immense value. Listening during held expiration w th the patient either lying flat or bent forward is tandard practice. Exercise often brings out doubtf l diastolic murmur Transiently induced systemic hypertension and reflex bradycardia, following an intravenous injection of phenylephrine is of great alue.[2,3] The raised diastolic pressure markedly intensifies and prolongs the murmur and the brad cardia makes timing easy However the administration of an intravenous injection is great disadva tage and discourages its routine pplicability

Squatting raises the systemic blood pressure by compressing the femoral arteries and retarding arterial run-off into the lower limbs. Although the rise in blood pressure is not great, it is sufficient to intensify and lengthen the very soft murmur of mild aortic incompetence and to give reasonable certainty to the diagnosis in the doubtful case. These murmurs lessen or even disappear pon standing but reappear on squatting I 9 out of 25 patients, the early diastolic murmur was the only abnormal ty In the others, the widened pulse pressure and hyperkinetic pulsations of aorta and left entricle on fluoroscopy strongly supported the diagnosis. In all these subjects, squatting intensified the murmur I 3 the murmur was missed by so examiners in the conventional postures, but was no doubt once squatting had brought obvious murmur

I patients with moderate or gross aor

t tion the blowing dia tolic murmur w often nch nged or only lightly increased on squatting. Th suggest that when aortic regurgitation is pro unced the modest rise blood pressure in duced b squatt ng does not ppreciably increase the regurg t t backflow. Fort nat ly the squatting tane er n red nd t in more severe degrees of ortic reg rg tation where l nic l diagnosis is usually simple

W therefore suggest that squatt g be added t the rou t ne bedside id l u lt tion nd mphasize t gre t lue m l t s nd t msify ng the rl d t lic murm k t tal nd m ld degrees d ortic reg rg t t

L. V o lpoel M.D. M.R.C.P.
M. Nellen M.I. F.R.C.P. F.R.C.P.(Edin.) F.I.C.C.
B k d S M.Med. M.R.C.P.
V. Sch M.Sc. Ph.D. M.D. F.R.C.P. F.R.C.P.(Ed), F.I.C.C.
C dio Cl ic Department of Medicine
U n t f C pe Town C.S.I.R.
Cardiova l P lm R earch Group
G oot Sch Hospital
C pe Town South Afric

REFERENCES

1. Nellen, M., Gotsman, M. S., Vogelpoel, L., Beck, W., and Schrire, V.: Effects of prompt sq tt ng on the systolic murmur in hypertrophic obstructiv cardiomyopathy, Brit. M. J. 3:140, 1967.
2. Besterman, E. M. M.: The use of phenylephrine to aid auscultation of early rheumatic diastolic murmurs, Brit. M. J. 2:205, 1951.
3. Vogelpoel, L., Schrire, V., Nellen, M., and Swanepoel, A.: The use of phenylephrine in the differentiation of Fallot tetralogy from pulmonary stenosis with intact ventricular septum, Am. Heart J. 59:189, 1960.

Auscultatory, pressure, and flow phenomena in late systole

Since the suggestion that mid tolic licks nd late systolic murm rs could orig nat from n trioventricula al abundant evidence t support this theory has been collected. At the same time emphasis has been given to the occurrence of mitral regurgita t murmurs that ha e late systolic accentuation. Why these events should take place at that time in sy tole ha remained obscure, however. Barlow has written, "There is certainly no haemodynamic reason for larger regurgitation during late systole since the gradient between left ventricle and left trium is decreasing t that time. In further paper Barlow and associates write, A increased mou t of regurgit tion in lat y tole must come from some natomic deformity of the mitral valve. There are sever l observ tions, however which enable one t mak reasonable theory concerning this timing, based not on anatomic, but on hemodynamic factors, from which mber of prediction follow that can be tested against present knowledge or future observation.

The first observation is that t the aortic valve in the dog, peak systolic pressure precedes peak flow by short interval, about 0.02 t 0.04 sec. This follow from inertia of blood. The same consider tion might pply t an incompetent mitral valve so that the point of maxim m amplitude of mitral regurgita t murmur might follow peak systolic pressure by a short interval because of this factor.

However in mitral incompetence the peak flow is appreciably arlier in the y tolic ejection period than in the normal situation, so that this possible reason for delay of maximum amplitude of the murmur beyond peak pressure cannot account in any way for the marked delays observed.

The more pertinent observations are contained in the work of Elkins and co-workers and of Rodbard and Williams. The former describe as characte i tic of the left ventricular pressure pulse in mitral competence a sharp fall i pressure from the systolic peak, and their figure 7 show this steepness as com timing until well dow the slope of the declining systolic pressure curve. In this same figure the left trial pressure curve is shown as having an increased pward slope beginning and ending at the same time the teep part of the downward slope of the ventricular pressure curve. Elkins and associates note "R pid decline in ventricular pressure occurred as left trial pressure rose steeply presumably as regurgitant flow wa greatest. Were the late systolic rise in left tri l pressure due entirely to decreasing left atrial distensibil ty one would expect not steepening of the coincident slope of the entricular pressure f ll, but the opposite.

Rodbard and Williams analyzed models the effects of having two orifices close to one another (as are the aortic and mitral orifices), so that fluid can pass through both. The models demonstrated interalia the following points: (1) that the greater the discrepancy in the size of the 2 orifices, the greater the share of fluid passing through the larger one; (2) that at constant ratio between the sizes of the 2 orifices, the greater the total flow rate and the less the share taken by the smaller one; (3) that if the flow rate through the smaller orifice is high, the phenomenon of flutter may occur in a slack-walled tube attached to it; (4) that the resistance of the chamber into which the fluid passes through the small orifice contributes significantly to the determination of how much fluid will pass into it, and also to the determination of how much passes through the larger orifice as well.

The second of these observations of Rodbard and Williams may be amplified. From physical principles it would appear that the mitral valve is more likely to see side pressure of the column of blood ejecting from the ventricle rather than pressure that would be recorded by a catheter or manometer placed in the lumen of the ventricle. The greater the flow of blood through the aortic orifice, the less this side pressure would be, and the increase in the share taken by the aortic valve is thus logical. Moreover, as Elkins and co-workers[5] show, the aortic flow in mitral regurgitation is shifted, so that more occurs in the earlier part of ejection, and peak aortic flow is increased. The hemodynamic response that would further decrease side pressure and therefore regurgitation during the rapid ejection phase is thus seen to occur presumably as the result of the operation of Frank-Starling mechanism. Also this response may slightly decrease mitral regurgitation in the isometric phase of contraction by shortening the duration of that phase. The operation of the general mechanism produces the result postulated by Braunwald and co-workers[6] who state that "hypodynamic systolic contraction would tend to augment mitral regurgitation." Moreover it agrees with the observation that after an ectopic ventricular beat, a late systolic murmur becomes pansystolic.

The situation as ejection falls will be quite different from that during rapid ejection. There is now a slowly moving column of blood, but ventricular pressure is at or near peak. The pressure of the blood as seen by the mitral valve is the same as the pressure anywhere in the ventricle—a static pressure. The ventricle is virtually converted into a one outlet system under high pressure. Mitral regurgitation must increase and the accompanying murmur must increase, or if the mitral incompetence was so minor that rapid ejection through the aorta made mitral regurgitation negligible or absent, then during reduced ejection mitral regurgitation would begin and be audible. Late accentuation of mitral regurgitant murmurs and late systolic murmurs are thus explained. One would expect also that as the mitral regurgitation increased in late systole, ventricular pressure would show a sharper decline, and left atrial pressure a sharper rise in late systole than normal, and the observations of Elkins and co-workers are thus explained. One can predict that the more collapsing the peripheral pulse is in mitral incompetence the more likely is late accentuation of the regurgitant murmur to be found. One can predict that if mitral incompetence accompanies subaortic muscular hypertrophy and stenosis, the regurgitant murmur will be late systolic.

The rapid increase in effective pressure against the mitral valve as aortic ejection failed would stretch the chordae tendineae and the midsystolic click would thus be explained and the term "chordal snap" further justified as a term descriptive of the origin of the noise, i.e., a mitral snap of its origin.

Pressure against the mitral valve therefore increases during ventricular systole to two peaks, one at the outset of ejection and one at the time ejection fails, and the peaks are separated by a trough caused by high flow through the infundibulum. Though factors such as papillary muscle contraction and shortening of the ventricular chamber may interfere, it may be expected that these changes in pressure would be reflected in chordal tension change. The findings of Salisbury and associates are interesting in this connection. In open-chest dogs chordal tension was found to rise to a peak at about the beginning of aortic ejection. It then fell but under some circumstances (aortic constriction and cutting other chordae) it rose again to a second peak, and finally fell when ventricular pressure fell. It seems reasonable that given the right values for ventricular pressure change, and for resistance to aortic and regurgitant mitral outflow, a sharp peak in chordal tension may occur in late systole, just at the time when chordal snaps are known to occur. The two peaks may even be responsible for snaps either from the same or different chordae, and changing values may shift a late chordal snap to the position of an ejection click.

Chordal snaps may tend to be associated with minor mitral incompetence not only because a chorda tendinea is then more likely to be elongated, but because in mitral incompetence the necessary conditions are present because of ventricular pressure rise and resistance to aortic and regurgitant mitral outflow.

The mechanism seems quantitatively feasible. Late systolic murmurs begin and chordal snaps occur predominantly in the second and third quarters of the ejection period, during which 70 to 75 per cent of the stroke volume is ejected. If the stroke volume is 80 ml. and ejection lasts 0.24 second, the flow rate in these quarters averages 500 ml. per second. The infundibulum narrows as systole proceeds[14] and at midejection it may have a diameter of 1.5 cm. Linear velocity through the infundibulum will be 282 cm. per second and kinetic energy developed will be equivalent to 29.5 mm. Hg. An apparent gradient of about 105 mm. Hg between left ventricle and left atrium would be reduced to about 75 mm. Hg. At the end of ejection no kinetic energy is developed, and the pressure gradient across the mitral valve will be perhaps 95 mm. Hg, so that the gradient has increased. The mitral valve leaflets form one boundary of the infundibulum, so that they are immediately sensitive to flow effects.

Late systolic murmurs are, as stated in the general theory, the result of minor mitral incompetence, and the common observation of this fact is ... Late systolic accentuation of mitral ...

murmur would similarly be a sign of relative insignificance of the mitral incompetence and of pliability of the relevant mitral leaflet the posterior. In fully developed rheumatic mitral regurgitation the immobility of the chorda-leaflet mechanism and the severity of the incompetence make late murmurs most unlikely. The chordal snap and late systolic murmur are, therefore, not features of this state. Excessively rapid aortic flow might, however, cause during ejection such reduction of otherwise significant mitral regurgitation that a uniform murmur became one accentuated in late systole. This leads to the prediction that an acutely induced increase in aortic flow early in systole should tend to convert a mitral pansystolic murmur of uniform amplitude into one that is quieter in early systole and accentuated in late systole, the softer pansystolic murmur of lesser incompetence into a late systolic murmur, and the late systolic murmur into a later one. On the contrary, an acutely induced decrease in aortic flow rate early in systole should tend to produce changes in the opposite direction. Drugs and positional changes may be used for increasing these changes.

Rodbard and Williams' third observation quoted above would lead one to expect that the phenomenon of flutter may be audible when mitral incompetence is minor, as this implies a narrow regurgitant orifice and one suitable therefore for the production of the phenomenon. Figure 8 of the paper by Barlow[4] shows a waxing and waning of a late systolic murmur which is consistent with this explanation. Rapid flutter may be expected to produce a musical murmur whose occurrence in late systole has been commented on.

The fourth quoted observation by Rodbard and Williams would allow two further predictions. First, that a small left atrium must be not only a result of minor incompetence but also a cause of it, and a large chamber equally both the result and cause of severe incompetence. Second, that progressive left atrial enlargement must exacerbate mitral incompetence without there necessarily being any change in the mitral valve, its chordae tendineae, or its ring.

The late systolic murmur increases in amplitude during inspiration and this has been explained as due to some change in the position of the heart. However, it has been shown[11] that the extrapericardial pulmonary vessels must be relatively easily distended by inspiration to account for the premature closure of the aortic valve early in inspiration in constrictive pericarditis. Inspiration in the absence of constrictive pericarditis would be expected to reduce even more the resistance to backflow of blood through the mitral valve, and so to increase this back flow. The late systolic murmur or accentuation would, therefore, increase in intensity on inspiration, and a positional change in the heart becomes an unnecessary explanation. These murmurs and any related chordal snap should begin earlier in systole during inspiration for the same reason, and the change in the case of the snap has been described.

Many of these observations and predictions may also be applicable to the right ventricle and tricuspid valve, but it is noteworthy that the distance between the tricuspid and pulmonary valves is greater than between mitral and aortic valves. Moreover, right ventricular pressure rises only to about 25 mm. Hg at peak pressure, so that the late systolic phenomena must be rare on the right side of the heart. Given the appropriate circumstances, however, due to anomalies such as septal defects which raise pulmonary artery flow and pressure, they may be expected to occur.

J. V. O. Reid, B.M., M.R.C.P.
Department of Physiology
University of Natal
Durban, Natal
Union of South Africa

REFERENCES

1. Reid, J. V. O.: Mid-systolic clicks, South African M. J. 35:353, 1961.
2. Barlow, J. B., Bosman, C. K., Pocock, W. A., and Marchand, P.: Late systolic murmurs and non-ejection ("mid-late") systolic clicks, Brit. Heart J. 30:203, 1968.
3. Barlow, J. B., Pocock, W. A., Marchand, P., and Denny, M.: The significance of late systolic murmurs, Am. Heart J. 66:443, 1963.
4. Barlow, J. B.: Conjoint clinic on the clinical significance of late systolic murmurs and non-ejection clicks, J. Chron. Dis. 18:665, 1965.
5. Spencer, M. P., and Greiss, F. C.: Dynamics of ventricular ejection, Circulation Res. 10:274, 1962.
6. Elkins, R. C., Morrow, A. G., Vasko, J. S., and Braunwald, E.: The effects of mitral regurgitation on the pattern of instantaneous aortic blood flow, Circulation 36:45, 1967.
7. Rodbard, S., and Williams, F.: The dynamics of mitral insufficiency, Am. Heart J. 48:521, 1954.
8. Braunwald, E., Welch, G. H., and Sarnoff, S. J.: Haemodynamic effects of quantitatively varied experimental mitral regurgitation, Circulation Res. 5:539, 1957.
9. Salisbury, P. F., Cross, C. E., and Rieben, P. A.: Chorda tendinea tension, Am. J. Physiol. 205:385, 1963.
10. Taloulas, T.: Calibre vibrations in the left ventricular outflow tract, Acta radiol. (diag.) 3:209, 1965.
11. Beck, W., Schrire, V., and Vogelpoel, L.: Splitting of the second heart sound in constrictive pericarditis, with observations of the mechanism of pulsus paradoxus, Am. Heart J. 64:765, 1962.

Letters to the Editor

Hematocrit after acute myocardial infarction

To the Editor:

The interesting article by Stables and others concerning the possible role of hemoconcentration in the etiology of myocardial infarction (Am. Heart J. 73:153, 1967) further supports the important finding that the hematocrit may be elevated in patients with an acute myocardial infarction. While this may have an aggravating effect, it does not necessarily follow that there is any etiologic relationship. Indeed, it is reasonable to postulate that the elevation in hematocrit is a result of the myocardial infarction. While the authors were very careful to control such extraneous influences on hematocrit as posture, exercise, etc., it is possible that myocardial infarction itself tends to raise the hematocrit. It is certainly well known that ventricular failure of greater or lesser degree may follow upon myocardial infarction. An acute elevation in either pulmonary or systemic venous pressure, even of mild degree, would effect an acute reduction in plasma volume. Patients with chronic heart failure are known to respond to exercise with a greater rise in peripheral venous pressure and drop in plasma volume than do normal persons (Gilbert, R. P., and Lewis, J. K., Circulation 2:402, 1950). The drop in plasma volume after myocardial infarction might also be the result of fluid loss from vomiting or from decreased oral intake during the first day or so following the acute infarction.

Thus far the phenomenon seems to be a real one. The nature of its relationship to the myocardial infarction needs to be established. This would seem to be a case for some prospective study.

Robert P. Gilbert, M.D.
Associate Dean
Jefferson Medical College
Philadelphia, Pa.

Reply

To the Editor:

We agree that the results of our investigation do not necessarily imply an etiologic relationship between an elevated hematocrit and myocardial infarction and that a prospective study is required. To quote from our article, "The exact role of hemoconcentration should be determined by a prospective study of the incidence of myocardial infarction in groups of subjects with high and low hematocrit values or by a controlled trial of regular venesection in the prophylaxis of myocardial infarction in patients with high hematocrit values" (Am. Heart J. 73:153, 1967).

No patients with overt cardiac failure were included in the study, nor did any of the subjects experience severe vomiting. We doubt if oral intake was decreased sufficiently to have been a factor producing a low plasma volume, but we cannot be sure about this, as the patients' fluid balances were not recorded.

D. P. Stables, M.B., F.C.P.(S.A.)
D 607 Forest Hill
Mowbray
Cape Town, South Africa

Electrocardiographic changes produced by thioridazine and chlorpromazine

To the Editor:

In his article (Am. Heart J. 76:153, 1968) Dr. Burda reported on the electrocardiographic changes of a patient who had ingested an estimated 5 Gm. of thioridazine.

He stated that the prolongation of the Q-T interval is the result of the broadened T wave. In our study (J. A. M. A. 198:16, 1966) we demonstrated that the morphologic change does not account for the increase in the duration of the Q-T. We concluded that there are two effects, one morphologic and the other a prolongation of the Q-T which may occur in persons receiving thioridazine or chlorpromazine at usual therapeutic dosage levels.

The author further stated that the U wave forms the distal hump of the notched or double-humped T wave. In our article referred to above, we demonstrated that the U wave does not form the distal hump of the T wave.

Furthermore, it is our experience that the T wave changes are not limited to the anterior septal leads, as indicated by Dr. Burda.

John R. Huston, M.D., Consultant to Research Lab.
George E. Bell, M.D., Director, Research Lab.
Columbus State Hospital
1960 W. Broad St.
Columbus, Ohio 43223

Reply

To the Editor:

Drs. J. R. Huston and G. E. Bell have presented evidence that thioridazine (Mellaril) prolongs the Q-T interval by one of two ways: (1) the appearance of morphologic T wave changes, characterized best as "rounding, blunting or notching," or (2) as a simple Q-T prolongation without a T or QRS change. When a U wave appears, it is fed

pendent of the morphologic T wave change[4] and does not form the distal hump of a notched T wave as referred t in earlier papers. The T wave changes may likewise be generalized nd it is not implied in my case tud that these hanges are limited t the septal are When T w ve n er son does occur it ma be most evident in the early precordial leads.

It h bee my experience th t chlorpromazine (Thorazine) w ll produce sim l T w ve changes and the Q-T interv l ma be further ncreased because of QRS prolongation as ha been previously observed experiment l mals and h man subject

Ch st pher D B rda M.D
1121 Louisiana Avenue
Shreveport La 71101

REFERENCES

1 Huston, J R nd Bell C F The effect of thioridazine hydrochloride d hlorpromazine on the lectrocardiogr J A M A 198 16 1966
2 Ban T A and St J A The effect of phenothiazines on the elect rcardiogram Canad M A J 91:537 1964
3 Ba T A d St J A Electrocardiographic hanges nduced b phenothiazine dosage Am He rt J 70:575 1965
4 Burda, C D Electrocard graphic bnormal ties induced b hioridazine (Mellaril) Am Heart J 76 153 1968
5 Kelly H G F J I d La ert S. G. Thioridazine h dr chloride (M llaril) Its effect on the electrocardiog ud report of two f talities w th lectrocardiogr phic bnormalities. Canad M A J 89:546 1963
6. Moyer J H and Ten Ba um quoted by Meduna, L J Gr upner K f and Murphree O D Electrocardiographic ha ges associated with the use of th ridaz ne J Neuropsychiat 5:344 1964

Electrocardiographic evaluation of LVH

To the Editor

The article by Liu nd DeCristofaro in the November 1968, America Heart Journal is a valuable contribution t the electrocardiographic recognition of LVH The uthors, however while referring in passing t other work bearing on the value of R omitted consideration of such criteria in their table of comparisons Indeed, while recognizing the discouraging inadequacy of voltage criteria, there is no indication as to how they arrived t a consideration of R as appropriate for study In fact, the basis for this was laid in remarks by Littman nd Griep[3] and later studied formally by Holt nd Spodick and Kumar nd Spodick. The latter tud ies demonstrated a very high specificity for the criterion R > Rv5, although its sensitivity was low In the first tudy the *specificity* was t least 76 per cent and in the second 88 per cent. Moreover it was shown that the absolut voltage was less important than the ratio of oltage between these leads in those cases of LVH in which R exceeded Rv5.

These remarks are intended as supplementary and not as serious criticism of the contribution of Liu and DeCristofaro. Their autopsy material as *far superior to ours* and was nicely handled. However it would have been of great interest to compare specificity of R ≥ 18 mm. with R > Rv5 in their excellent series. Moreover the contribution of Littmann in first recognizing the importance of R should be noted

David H Spodick, M.D
Director Cardiology Division
Lemuel Shattuck Hospital
170 Morton St.
Boston M ss. 02130

REFERENCES

1 Liu C. K., and DeCristofaro, D Sensitivity and specificity of electrocardiographic evaluation of LVH in 364 nselected autopsy cases. Am. Heart J 76:596, 1968
2 Holt, D H and Spodick, D H: The Rv6 R voltage ratio in left ventricular hypertrophy Am Heart J 63:65 1962.
3. Griep, A. H Pitfalls in the electrocardiographic diagnosis of left entricular hypertrophy Circulation 20:30 1959 (Includes remarks by Littma n.)
4 Kumar S and Spodick, D H. Specificity of Rv > R in the electrocardiographic recognition of left entricular hypertrophy Dis. Chest 50:519 1966

Reply

To the Editor

W appreciate Dr Spodick comments on the paper "Sensitivity and specificity of electrocardiographic evaluation of LVH in 364 unselected autopsy cases A criterion Rv6 ≥ 18 mm. as proposed" (Am. Heart J 76:596, 1968).

Four questions were raised in reference to the paper (1) Why was the ratio of Rv6/Rv5 ≥ 1 omitted in our comparative evaluation of voltage criteria for LVH?" (2) I the ratio of Rv6/Rv5 not more sensitive than the absolute voltage of R alone? (3) How wa R ≥ 18mm. arrived at as a criterion? (4) Should not Littmann receive recognition for first recognizing the importance of Rv6 as a criterion for LVH?

The ratio of R v/Rv ≥ 1 was initially considered in our pilot study but was eliminated because of the large number of false positives. Table I show that the ratio of Rv6/R greater or equal to one in our study had a value of 24 per cent false positives in 145 control subjects, whereas the Authors' criterion of R ≥ 18 mm. had only 7 per cent false positives. The Authors criterion had sensitivity of 24 6 per cent in 145 documented cases of LVH as compared with sensitivity of 18.6 per cent in the same LVH group and marked decrease in specificity to 75 per cent when the Rv/Rv5 ratio as used.

Table I. Sensitivity of various LVH criteria

Criteria	Left ventricular hypertrophy 145 pts										Control 145 pts.		Intermediate 56 pts	
	Pure LVH 60 pts.		LVH and RVH 39 pts.		LVH and MI 37 pts		LVH RVH, and MI 9 pt		Total 145 pts		False positive		(?) False positive	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Author $R_{V6} \geq 18$	13	22 0	11	28.2	8	22.0	4	44 4	36	24 6	10	7 0	4	7 1
Holt $R_{V6}/R_{V1} \geq 1$	8	13.5	9	23 0	7	19 0	3	33 0	27	18.6	35	24 0	7	12.4
Authors $R \geq 17$	18	30	10	25.6	9	4 0	3	33	40	27 6	15	10.3	5	9 0
Authors $R_{V6} \geq 19$	11	18	9	23.0	7	19 00	0	0	27	18 6	9	6 1	2	3.6

Abbreviations: LVH, Left ventricular hypertrophy; RVH, right ventricular hypertrophy; MI, myocardial infarction.

Table II. Sensitivity, specificity, and predictive values of selected ECG LVH criteria

Criteria	LVH 145 pts	Control 145 pt	Sensitivity (%)	Specificity (%)	Predictive value—positive (per cent)	Predictive value—negative (per cent)
Authors $R_{V} > 18$	36	10	24 6	93 1	78 3	54 1
$R_{V6}/R_{V1} \geq 1$	27	35	18 6	75 0	43 5	49 0
$R \geq 17$	40	15	27 6	89 6	72 7	55 3
$R \geq 19$	27	9	18 6	93 8	75 0	53 5

We arrived at R ≥ 18 mm. after an analysis of various absolute voltages of R (Tables I and II) indicated which value would give the greatest sensitivity but maintain specificity of over 90 per cent. $R_{V6} \geq 17$ was also considered as criterion because of its high sensitivity but had less specificity and, therefore, could increase the frequency of false positives. However R ≥ 17 still remains an excellent criterion compared to the other criteria discussed in the paper and could be used as criterion for the electrocardiographic diagnosis of probable LVH.

Dr. Spodick referred to the paper of Griep[2] where a personal communication with Littmann was made suggesting that an R of greater voltage than R might indicate the presence of gross left ventricular hypertrophy. We have found that this ratio is less sensitive and less specific than the absolute value of $R_{V6} \geq 18$ mm. (Tables I and II).

Nevertheless, it is disconcerting that utilizing all the commonly used ECG criteria for LVH we can accurately predict LVH in less than 50 per cent of the cases!

Chi Kong Lin, M.D.
Department of Medicine, Division of Cardiology
Harbor General Hospital
1000 West Carson St.
Torrance, Calif. 90509
Dominic DeCristofaro, M.D.
UCLA School of Medicine
Los Angeles, Calif. 90024

REFERENCES

1. Holt, D. H., and Spodick, D. H.: The R R voltage ratio in left ventricular hypertrophy, AM. HEART J. 63:65, 1962.
2. Griep, A. H.: Pitfalls in the electrocardiographic diagnosis of left ventricular hypertrophy, Circulation 20:30, 1959. (Includes remarks Littmann.)

Book reviews

CARDIOVASCULAR SURGERY 1967 Edited by C. Frederick Kittle, M.D. New York, 1968, The American Heart Association Inc 217 pages. Price $3.00

The Surgeons of the Council on Cardiovascular Surgery of the American Heart Association have been very active in keeping up to date monographs on cardiovascular surgery. This publication briefly defines the practical problems and advances for 1967. The monographs should interest cardiologists as well as cardiac surgeons.

ADVANCES IN MICRO-CIRCULATION Edited by H. Harders, Basel, 1968 S. Karger AG 160 pages. Price $12.75

This is the first volume on advances in microcirculation. It is devoted to microcirculation of bone marrow, peripheral nerves and exocrine pancreas. This short monograph is excellent. The illustrations are very good. The text clearly presents a good summary of the present state of knowledge on the subject. This monograph is highly recommended.

A TECHNIC FOR EXTRACORPOREAL CIRCULATION By Raymond C. Stofer D.V.M. Springfield, Ill. 1968, Charles C Thomas, Publisher 115 pages. Price $6.75

This is a brief presentation of the technique and principle of extracorporeal circulation. The discussions are extremely brief and the illustrations fairly good. Unfortunately the only way to learn the technique is to work with the equipment and participate in the procedure. Open heart surgery requires team work and the procedures, equipment, and activities vary with the team. This book can be of some assistance to the beginner.

ESSENTIALS OF CARDIOLOGY Ed. 2, by S. G. Owen, M.D. T. B. Stretton, M.B. and J. Vallance-Owen, M.A., M.D. Philadelphia, 1966, J. B. Lippincott Company 226 pages. Price $7.25.

Owen Stretton, and Vallance-Owen have attempted to do what many clinicians have thought could be done, that is, write a book on cardiology in about 200 small pages and still cover the essentials of the entire field adequately. Regardless of how noble the attempt, the reader who really needs the use of a book will always be concerned about the adequacy of such a synopsis. Although the authors have succeeded in writing a concise short book on the subject, they have made available a book, but for whom? Would this be recommended to medical students, interns, residents, or practicing physicians. This reviewer says no. The information is too brief and the subjects are not discussed sufficiently for any of them. This would apply to any portion of the book. In fact, the only one who could find the book useful is the well-trained cardiologist who wants to learn of some of the opinions of the authors, but whose knowledge is so extensive that he would appreciate that there is much more important information necessary to treat properly a patient with heart disease. This book might be useful to beginners.

Books received

ENCYCLOPEDIA OF MEDICAL RADIOLOGY By L. Diethelm, O. Olsson, F. Strnad, H. Vieten, and A. Zuppinger Berlin, 1968 Springer Verlag 1011 pages. Price 184.00.

HUMAN EMBRYOLOGY ed. 3. By Bradley M. Patten, New York, 1968, McGraw Hill Book Company Inc., 651 pages. Price $17.50.

ILLUSTRATED MANUAL OF LABORATORY DIAGNOSIS. By R. Douglas Collins, Philadelphia, 1968 J. B. Lippincott Company 299 pages Price $22.50

MODERN TREATMENT Vol. 5 No. 4 July 1968 (1) Treatment of Fluid and Electrolyte Imbalance, by David D. Thompson, (2) Current Treatment of Clinical Tetanus, by Norman A. Christensen and Deloran L. Thurber New York, 1968, Paul B. Hoeber Inc., Medical Book Division of Harper and Row Publishers, Inc., 1500 pages per year Price $16.00.

DEATH AND CONTEMPORARY MAN: THE CRISIS OF TERMINAL ILLNESS. By Carl G. Carlozzi, Grand Rapids, Mich., 1968 W. B. Eerdmans Publishing Co., 79 pages. Price $1.45.

DIE BEDEUTUNG DES VERHALTENS DER KRANKEN GOMEN UNTER KORPERLICHER ARBEIT FUR PROPHYLAXE UND REHABILITATION By Bernhard Luderitz and Walter Noder Koln and Opladen, 1968, Westdeutscherverlag 38 pages.

EVALUATION OF RESULTS OF CARDIAC SURGERY American Heart Association Monograph No. 22. By Lewis Dexter and Lars Werko Report of a Symposium of the Fifth World Congress of Cardi-

ogy November 3 1966, New Delhi, India, New York, 1968, American Heart Association, 112 pages. Price $1.00

THE HEART IN HEALTH AND DISEASE. By Rustom Jal Vakil, Bombay 1968, University of Bombay 111 pages.

HYPERTENSION, VOL. XVI NEURAL CONTROL OF ARTERIAL PRESSURE. By J. Edwin Wood, M.D. Proceedings of the Council for High Blood Pressure Research, American Heart Association, Cleveland, November 10-11, 1967 New York, 1968, American Heart Association, 119 pages. Price $3.00

MEDICAL BASIS FOR COMPREHENSIVE COMMUNITY STROKE PROGRAMS. By Nemat O. Borhani and John S. Meyer in Collaboration with the Special Task Force of the Joint Council's Subcommittee on Cerebrovascular Disease (National Heart Institute and National Institutes of Neurological Diseases and Blindness), National Institutes of Health, June 1, 1968 For copies write Dr. Jerome G. Green Executive Secretary Joint Council Subcommittee on Cerebrovascular Disease, NHI-NINDB National Institutes of Health, Bethesda, Md. 20014

DIARY OF A HEART PATIENT. By Yehuda Kesten, New York, 1968 McGraw-Hill Book Company Inc., 272 pages Price $5.95.

HERZCHIRURGIE BEIM SÄUGLING UND KLEINKIND. By Hans Schwarz, New York, Berlin 1968 Springer Verlag, 138 pages. Price $11.25

THE HUMAN BRONCHIAL CIRCULATION IN HEALTH AND DISEASE. By Leon Cudkowicz, Baltimore, 1968 The Williams & Wilkins Company 424 pages Price $18.00

KARDIOLOGISCHE FRAGEN IN DER PÄDIATRIE—22 POSTGRADUATE COURSES IN PEDIATRICS. Edited by E. Rossi, New York Basel, 1968, S. Karger AG 150 pages. Price $9.35

Announcement

The Sixth International Tissue Conference, entitled Blood Cell Tissue, will be held at the Lankenau Hospital Philadelphia, Pa. on Oct. 30 through 31 1969. The following topics will be discussed: regulatory mechanisms, metabolism and function of normal and abnormal cells, and recent development in therapy. For further information please contact William L. Holmes, Ph.D. Division of Research Lankenau Hospital Lancaster and City Line Avenues, Philadelphia, Pa. 19151.

American Heart Journal

June 1969 Volume 77 Number 6

Editorial

How normal is the donor heart?

N P DePasquale M.D
G E. Burch M.D
New Orleans La

Electrocardiographic abnormalities associated with cerebrovascular stroke were first reported from this laboratory in 1954 These abnormalities consisted of deep inversion of the T wave, widening of the T wav increased amplitude of the U wave, prolongation of the Q-U interval, and bradycardia. Since the original publication, umer us reports have appeared which confirm the boor mal electrocardiographic pattern (CVA pattern) in patients with cerebrovascular accidents. I most reports the cerebrovascular accident was the result of subarachnoid hemorrhage although in some patients t as due to cerebral thrombosis. However have observed the CVA pattern following traumatic brain injury grand mal seizures, and cardiac syncope (Stokes-Adams syndrome) as well as in patient ith encephalitis, brain tumor and meningitis.

The pathogenesis of the CVA pattern is nknow It is unlikely that the abnormal T aves are due t atheromatous coronary artery disease, because the T wave inversion is not of the type characteristic of ischemic heart disease and the T abnormal ties has been noted to disappear after ecovery from the cerebrovascular accident. Experimental studies have shown that the CVA pattern may develop after electric stimulation of the posterior hypothalamus, intracranial injection of autologous blood, embolization of the carotid artery and mechanical increase in cerebrospinal fluid pressure W have postulated that the T-wav abnormalities associated ith cerebrovascular accident are related xtensive sympathetic activity (sympathetic storm) Autopsy studies of the hearts of patient d ing of cerebrovascular stroke hav demonstr ted patch areas of round cell infiltr tion and m ocardial degeneration as well as subendocardial areas of petechial and/or confluent hemorrhage. This latter finding is lso common in the hearts of patien h received nor epinephrine infusion prior to death It should be noted that the CVA pattern in the electrocardiogram is consistent th subendocardial injury Thus, the m ocardial injury associated ith cerebrovascular accident may be considered as a neurogenic or catecholamine-induced cardiomyopathy I this re gard, T wa e abnormalities similar to those observed in patients ith cerebrovascular accident have been produced by infusion of catecholamines directly into the coronary arteries of experimental animals.[12] That fairly extensiv and diffuse morphologic changes were produced in the myocardium by central nervous system injury as clearly established in mice by intracra ial jection of small volume (<0 01 c.c) of blood

Whatever the cause of the subendocardial injury nd the electrocardiographic abnormalities in patients ith cerebrovascular accident it is important to recognize that hearts selected for cardiac transplant are often obtained from patients ho have suffered extensiv central nervous system damage, usually secondary to subarachnoid hemorrhage or traumatic brain injury It is not unreasonable t assume that t heart in some instances, myocardial injury is present in donor hearts obtained from patients ith extensive brain damage. Obviously such injury ould be superimposed upon whatever structural and biochemical alterations occurred dur ing the terminal illness. I this egard, it is sometimes forgotten that pharmacologic agents particularly pressor amines, may damage heart muscle. I addition, hypoxia, lectrolyte disorders, and acid-base imbalance, all common events during terminal illness, may produce heart muscle injury

Inasmuch as neurogenic cardiomyopathy may occur secondary to brain injury nd toxic or metabolic cardiomyopathy may occu during terminal illness in association with drug therapy lectrolyte disorders, and acid-base imbalance, it is reasonable t assume that a heart removed from donor ith

From the Department of Medicine, Tulane University School of Medicine, New Orleans, La

Table I. Electrocardiographic classification of patients studied

Clinical diagnosis	Age	Race N	Race C	Sex (No.)	ASHD (No.)	HHD (No.)	HASHD (No.)	PMD (No.)	RHD (No.)	Total
Normal (ECG and clinically)	29 to 70	2	6	M						8
Left ventricular hypertrophy	37 to 73	8	9	M	3	5	5	2	2	17
Right bundle branch block	37 to 73	3	1	M	1		2		1	4
Left bundle branch block	61 to 67	0	2	M	2					2
Myocardial infarction, old	37 to 78	2	10	M	9		3			12
Organic heart disease with T wave inversion	37 to 76 (Mean 54)	5	5	M	3	3	3	1		10
No heart disease with T wave inversion	28 to 50 (Mean 41)	4	6	M						
obesity										3
hemorrhoid										1
cirrhosis										2
normal										3
asthma										1
Total										10
Toxic reaction	83		1	M	1					1
Total										64

Abbreviations: ASHD, arteriosclerotic heart disease; HHD, hypertensive heart disease; HASHD, hypertensive arteriosclerotic heart disease; PMD, primary myocardial disease; RHD, rheumatic heart disease.

Two hours after breakfast all patients had a base line 12 lead ECG. They were then given 10 Gm. of potassium chloride in a 25 per cent solution mixed with 6 ounces of fruit juice. Twelve-lead ECG's were taken at intervals of 1, 1½, and 2 hours after the ingestion. Following potassium administration only those ECG's with a substantial change in the direction of the T axis, sufficient to cause T waves to become upright in at least two leads, were scored as positive (Figs. 1 through 4). Lesser changes were scored as negative. Changes in contour of the T wave without change in direction were scored as negative (Figs. 5 and 6).

Results

As indicated in Table II, T changes after potassium administration were manifested in none of the 8 normal subjects, and in only 2 of 35 patients with classic electrocardiographic changes of left ventricular hypertrophy, bundle branch block, or myocardial infarction (Figs. 7 and 8). The ECG's of the most important group, those with nonspecific T wave changes, demarcated clearly after potassium administration. The ECG's of the 10 clinically normal patients reverted to a normal T-wave pattern. None of 10 with objective clinical

Table II. T wave changes after K^+

Diagnosis	No. of cases	No. with T wave change after K^+
Normal (Clinically and ECG)	8	0
Left ventricular hypertrophy	17	1
Bundle branch block	6	1
Myocardial infarction, old	12	0
Non-specific T wave inversion with heart disease	10	0
Non-specific T wave inversion without heart disease	10	10
Not completed (toxic reaction)	1	0
Total	64	

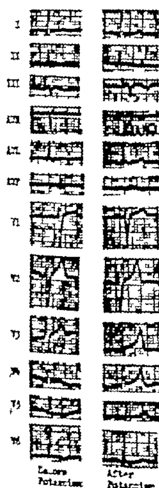


Fig. 1 Nonspecific T wave changes. No organic heart disease

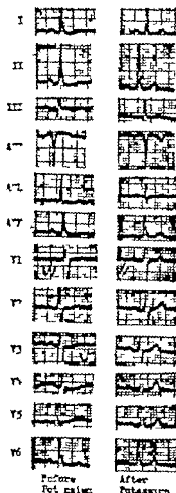


Fig. 2 Nonspecific T-wave changes. No organic heart disease

evidence of heart disease showed such a change.

Patient tolerance of the drug was good in general. Some patients commented on the extreme salty taste but were willing to take the drink. A few patients vomited shortly afterwards, but were able to retain the solution when tried later with sugar added. As shown in Fig. 5, in one patient the P-R interval increased from .20 to .26 after potassium.

One serious reaction occurred in the oldest patient in the group. This patient, 83 years old, survived an acute myocardial infarction in January despite shock and ventricular tachycardia. He was admitted to the hospital in July with congestive heart failure, right bundle branch block, first degree A-V block, and frequent ventricular premature contractions. He was treated with digitalis and procaine amide and did well. On November 4, he was given 10 Gm. of potassium chloride. Thirty minutes later he developed sinus arrest and asystole 5 to 6 seconds in duration alternating with groups of 3 to 4 idioventricular beats. He responded well to brief external cardiac massage and external pacemaking, returning to his previous rhythm. Six hours later he again had a prolonged asystole and responded to brief external massage promptly, resuming with a sinus bradycardia, again with first degree A-V block and right bundle branch block. On November 4, before potassium loading, serum potassium was 3.6, blood urea nitrogen (BUN) was 29; on November 5 it was 5.0, BUN was 31; on Nove

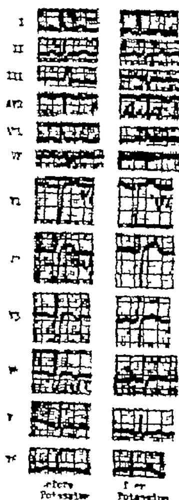


Fig. 3 Nonspecific T wave changes. No organic heart disease

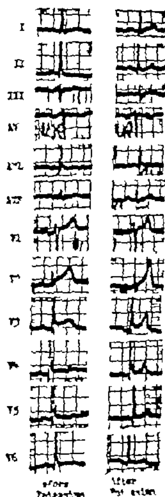


Fig. 4 Nonspecific T-wave changes and premature repolarization. No organic heart disease.

potassium was 4.3 BUN was 27 On December 20 six weeks after the potassium loading the patient survived his third episode of asystole and external massage once more resuming his prior rhythm and conduction defect. On December 29 an endocardial catheter was placed in position and functioned as pacemaker thereafter The patient succumbed to ventricular fibrillation on January 7 Attempts to defibrillate were unsuccessful.

Discussion

Electrocardiographic studies on large numbers of normal subjects were made in 1943 by Viscidi and Geiger [6] in 1944 by Graybiel and associates [7] Stewart and Manning [8] and Thomas.[9] These studies, largely spurred by the opportunity and need to evaluate the physical status of large groups of young men during World War II demonstrated a surprisingly high frequency of so-called abnormal records, presumably due to a largely unspecified variety of emotional and physical factors in individuals with clinically normal hearts.

Averill and Lamb[10] and Hiss et al.[11] in 1960 reported electrocardiographic findings in 67,375 asymptomatic individuals, 90 per cent between the ages of 20 and 40 Nonspecific T wave changes occurred in 581 of these healthy patients (0 86 per cent) The authors indicated the difficulty of separating T wave changes secondary to organic heart disease from those occurring without heart disease Hiss et al catalogued the different patterns of T wave abnormalities by amplitude configuration, and lead involvement. They found one pattern (low amplitude T in limb leads and low ampli

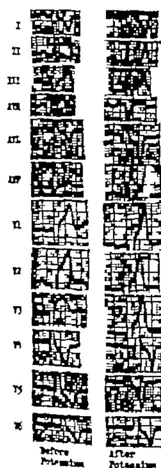


Fig. 3. Increased amplitude of positive and negative T wave deflections after potassium. P R prolongation.

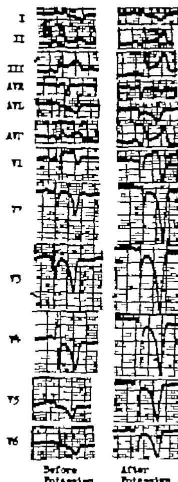


Fig. 4. Increased amplitude of negative T waves after potassium.

ble or inverted T in lateral precordial leads without increase in QRS-T angle (21.9 per cent]) increased significantly with age, and suggested this pattern may be indicative of organic disease. Other common patterns were low T less than .2 mv (17.9 per cent) left rotation of T vector in frontal plane without left rotation of QRS vector producing a wide QRS-T angle with a T axis less than 0 degrees (9.5 per cent) wide QRS-T angle with decreased T amplitude (40 1 per cent) Increased weight and increased heart rate correlated with T-wave changes. The median T axis in normal subjects was +45 degrees in abnormal subjects, 0 degrees.

Scherf[11] in 1946 compiled an extensive list of factors other than heart disease which are associated with S-T segment and T wave changes similar to those of coronary sclerosis and myocardial fibrosis drugs (digitalis quinidine quinine epinephrine atropine, mecholyl nicotine, and emetine) exercise, acute infections (influenza, pneumonia tuberculosis, typhoid typhus diphtheria, trichinosis, and brucellosis) pericarditis, metabolic disorders (obesity hyperthyroidism fever acidosis, alkalosis hypoglycemia hyperventilation serum sickness, thiamine deficiency nicotinic acid deficiency acute blood loss, chronic anemia, and carbon monoxide poisoning) renal disease upper abdominal disease (pancreatitis gall bladder disease, and peptic ulcer) pulmonary embolism and autonomic nervous system dysfunction (anxiety and fear) He suggested the effect of emotion is mediated from the central nervous n

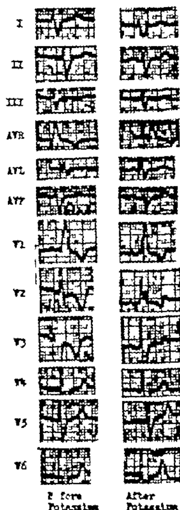


Fig 7 Right bundle branch block with positive T wave response t potassium.

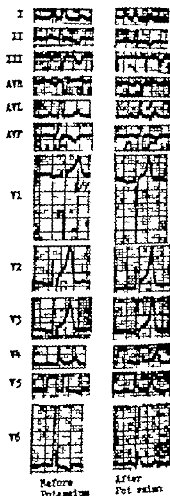


Fig 8 Left ventricular hypertrophy with positive T-wave response to potassium

the vagus sympathetic nerves to the coronary circulation and conduction mechanism

Other authors[1-40] have ascribed T wave changes to a variety of similar noncardiac conditions. Additional causes have been cited by Goldberger[41] (carbohydrate ingestion) Wasserburger[42-44] (hyperventilation and anxiety) Hiss et al[45] (orthostatism, breath-holding hyperventilation and atropine) and Kiessling and associates[47] (body position hyperpnea, emotion cold drinks, spontaneous pneumothorax, and hypothyroidism)

Wasserburger[34-38] investigated the T inversions in precordial leads found in children some adult Caucasian males and 10 per cent of adult Negro males (juvenile pattern) Following hyperventilation T inversions were seen in 13 per cent of Negroes and 9 5 per cent of Caucasians. This pattern reverted to normal with potassium or Pro-banthine In adults with normal ECG s, T inversions occurred in 37 of 350 subjects with hyperventilation The inversion was blocked in 8 of 11 patients with Pro-banthine and in 6 of 6 with potassium Wasserburger concluded these effects may result from a vagal reflex arising in the thorax on hyperventilating

Mason[48] evaluated autopsy specimens of 270 young men who suffered accidental deaths. All had been asymptomatic for coronary artery disease. The age range was 17 to 42 with a mean of about 27 Macroscopic disease was found in about one third indicating that even in very young adult males the possibility of coronary ar

tery disease with consequent ECG changes must not be lightly dismissed.

Kiessling and associates[27] emphasized that some nonspecific T wave changes are due to coronary artery disease. He noted a higher death rate in individuals with nonspecific T changes than in a control group with normal ECG's. He stated that there is now no way to separate T changes due to coronary artery disease from those due to other causes.

In an early paper (1938) Winkler and coworkers[29] studied the electrocardiographic changes and serum potassium concentration following intravenous injection of potassium chloride. Brown and associates[30] reported serum levels after an oral dose of 8 Gm. of potassium salts (potassium citrate and potassium chloride). Patients without heart disease responded with an increase in serum potassium from 4.4 to 5.5 mEq. per liter. Those with heart disease but without congestive heart failure rose from 4.4 to 6.8; those with heart disease and in failure rose from 4.7 to 7.4. High potassium levels occurred sooner and were sustained longer in patients with heart disease and occurred soonest and were sustained longest in patients with heart disease and in failure. Wendkos[31] gave 10 Gm. doses (5 Gm. of potassium acetate and 5 Gm. of potassium citrate) orally and noted an average rise in serum potassium of 1.1 mEq., with a minimum increase of 0.4 mEq. and maximum increase of 2.4 mEq. He found no relationship between the degree of serum potassium increase and rectification of the abnormal T wave, and postulated correction of myocardial cytokalipenia.

There has been a difference of opinion concerning the value of potassium administration in separating functional and organic T-wave abnormalities. Five authors suggest the test is of no use. Sharpey-Schafer[3] stated that inverted T waves were returned to normal by induced hyperpotassemia in 5 patients with left ventricular preponderance (secondary to hypertension or aortic stenosis) and in 4 patients with right ventricular preponderance (secondary to pulmonary disorders). However, he employed doses of a potassium chloride-potassium citrate mixture of no less than 15 Gm. and as much as 20 Gm. Bryant[4] supported this point of view in patients with hypertensive cardiovascular disease. He used between 5 and 20 Gm. of potassium citrate, potassium chloride, or potassium dibasic phosphate in 25 hypertensive patients with left ventricular hypertrophy and in 10 normal patients. He stated, "In the vast majority of cases the T wave became less inverted or upright when it was originally inverted or taller when it was originally upright. In a few instances the T wave became more deeply inverted. . . . In normal patients the administration of potassium was followed by ECG changes similar in character but less pronounced." There is not, however, in the published data further categorization of these findings into those with changes in the direction of the T axis as against those with changes only in magnitude, nor is there a correlation made with specific dosage within the wide range employed.

Schlachman and Rosenberg[7] utilized a mixture of potassium chloride, potassium citrate, and potassium bicarbonate. They wrote that potassium salts are capable of causing an upright deflection of organically inverted T waves and therefore will not differentiate the organic from the functional T waves. Of their 31 patients, 25 were hypertensive with left ventricular hypertrophy, 5 had myocardial infarctions, and 1 had aortic insufficiency. A total of 21 of the 31 patients received between 12 and 16 grams of potassium; the other 10 received between 5 and 10 Gm. Analysis of their data in terms of the criteria used in the present study reveals, despite the somewhat higher dosage, only 3 of the 31 patients had a T axis shift sufficient to revert T waves to upright in at least two leads. Of the remaining 28, 6 had T wave reversion to normal in one lead; the other 22 had no changes at all.

Dodge and associates[8] stated that amounts less than 15 Gm. of potassium chloride failed to produce significant ECG changes. They felt the administration of large doses of potassium would not correct the abnormal T vector (wide QRS-T angle) of myocardial infarction, ischemia, or left ventricular hypertrophy and would favorably affect the negative T patterns induced by metabolic or functional disorders, but that the high incidence of severe toxicity made the test too dangerous for routine

clinical use Sleeper and Orgain[22] abandoned the use of potassium as clinically impractical they gave only 20 mEq of potassium chloride intravenously to 6 patients.

Favorable results have been reported by Boyadjian and associates[23] Wasserburger and Corliss and Wendkos.[25] Boyadjian and coworkers using an 8 Gm potassium mixture reverted the ECG s of all 15 patients with functional T abnormalities to normal while none of 10 patients with organic T wave abnormalities showed changes. Wasserburger and Corliss using a mixture of 5 Gm of potassium citrate and 5 Gm of potassium bicarbonate corrected 60 of 60 functional T abnormalities but improved only 7 of 40 with myocardial infarction 5 of 40 with acute myocardial ischemia none of 10 with left bundle branch block, 4 of 12 with left ventricular hypertrophy none of 2 with pericarditis and none of 10 with digitalis effect. He concluded the test was clinically useful to distinguish functional and ischemic T changes. Wendkos states that benign repolarization disturbances are uniformly abolished by potassium (40 of 40) whereas morphologically similar T wave abnormalities due to cardiac pathology persist (none of 10 rectified)

Potassium loading is of special value in the occasional patient with both early repolarization and functional T wave abnormalities. The ECG s of these individuals with combined S-T segment elevation and T inversion may be diagnosed incorrectly as acute myocardial infarction or pericarditis. Potassium readily reverts their T waves to normal Two such patients are included in this study The S-T segment elevations particularly common in young Negroes, will often return to the base line with exercise[26]

While the role of potassium in clinical cardiology particularly in the treatment of digitalis intoxication is well known the specific mechanism of action of potassium in the myocardial cell and at the cell membrane is more obscure The fact that reversion to normal of inverted T waves following potassium administration reflects altered repolarization seems likely

Prinzmetal[27-44] and Sodi Pallares[1,4] have studied transmembrane potassium gradients with emphasis on resultant S-T segment changes. Prinzmetal found that severe ischemia led to potassium loss across the injured cell membrane (hypopolarization) with S-T segment elevation while mild ischemia induced increased potassium uptake (hyperpolarization) and S-T segment depression Sodi Pallares noted that the high permeability of potassium permits its dominance of the transmembrane potential Intracellular potassium/extracellular potassium (K_i/K_e) = 30/1 yielding a normal resting membrane potential (polarized state) of 70 to 100 mv Harris[45] reported that in the center of the infarct zone in dogs K_i is reduced 80 per cent on the seventh day after coronary occlusion reducing the K_i/K_e to 6/1 and reducing the potential difference across the membrane to less than 50 mv below which cardiac fibers become unexcitable[46] In the injury zone the decrease in resting membrane potential is less than in the infarcted zone. In the ischemic zone the final K_i/K_e ratio or state of diastolic polarization is normal. The recovery process, however is prolonged During recovery potassium crosses the cell membrane into the cell and sodium is extruded. The mechanism by which ischemia or other factors affect repolarization and the T wave has not been clearly elucidated Sodi Pallares has applied these concepts by treating acute myocardial infarction with an intravenous glucose-insulin potassium solution with resultant rapid return of elevated S-T segments to the base line and improved pathologic findings in experimental animals.

It seems evident that re-establishment of the normal resting transmembrane gradient is critical to repolarization When the ability to maintain the gradient is disturbed by anoxia potassium loading will usually not enable the membrane to support a difference in potential across it. When the gradient across the membrane is altered in an undefined manner by nonorganic factors, potassium loading will transiently re-establish the potential difference and, thereby temporarily change the T axis.

Wasserburger s patients tolerated 10 Gm. of oral potassium salts very well on the whole Two patients who took the potassium in a fasting state had transient nausea and vomiting and epigastric burning[1] One patient had transient trigeminal rhythm.

One patient received potassium 9 hours after an episode of acute ischemia of the anterior wall. Thirty minutes later he had multifocal ventricular premature contractions, then ventricular tachycardia and peripheral vascular collapse. Eight minutes later normal sinus rhythm spontaneously resumed.

Dodge's cases received higher potassium doses (15 Gm. of potassium chloride) and nearly all had nausea, vomiting, or epigastric burning. Half the patients experienced numbness and tingling of the extremities and circumoral region and diaphoresis. One patient noted muscle weakness. One patient with rheumatic carditis and mild congestive heart failure developed a sinus tachycardia, dyspnea, and paresthesias. Three patients with infarctions or left ventricular ischemia had transient substernal pain with ECG changes (S-T segment shift, enlarged T-negative area, or transient intraventricular conduction defect). There was one fatality, a 47 year-old Caucasian male with a history of dyspnea on exertion for 9 years, intermittent claudication for 3 years, and prior T inversions in Leads I and V_{1-4}. One hour after receiving 15 Gm. of potassium chloride by mouth he developed ventricular tachycardia and died 20 minutes later in ventricular fibrillation. Dodge did not record any instances of atrial standstill, atrioventricular, or intraventricular block. Schlachman and Rosenberg had one hypertensive patient who developed the Wenckebach phenomenon 30 minutes after potassium administration (1.4 Gm. of mixture) which lasted 2 hours, and one hypertensive patient who developed an A-V nodal rhythm 60 minutes after potassium (16 Gm.) was given. Brown observed nausea and vomiting, numbness and tingling, prolonged A-V conduction, and A-V block.

In the opinion of Wendkos, who used a 10 Gm. dose, the procedure is quite safe if the patients are not over age 60 and do not have a recent myocardial infarction or overt myocardial ischemia, congestive heart failure sufficient to decrease renal function, and renal impairment.

It is evident from this accumulated experience and the results of the present study with the potassium loading tests that serious reactions have occurred in those patients with obvious pre-existing myocardial disease for whom the test would not be advisable. It must also be emphasized that the potassium loading test is contraindicated in the presence of an elevated serum potassium or BUN or diagnosis of renal disease.

Conclusion

It is clear that the results presented support the opinion of Boyadjian, Wasserburger and Corliss, and Wendkos that the oral administration of a single dose of about 10 Gm. of potassium salts is quite reliable in the empiric separation of nonspecific T abnormalities not due to organic heart disease from those due to organic disease. All four studies used fairly similar doses of oral potassium. The difference in results between these studies and others in which repolarization changes were produced in a wide variety of organic conditions can be related to dose, mode of administration, and criteria used in evaluation of changes. The test is chiefly useful in patients with little or equivocal evidence of heart disease. Patients with a documented history of heart disease, overt positive physical findings, or ECG abnormalities, such as conduction defects or significant Q waves, do not need this test to establish a diagnosis of heart disease and should not receive it, as the test may be hazardous for this group.

Summary

The oral administration of 10 grams of potassium chloride in a single dose has been found to restore repolarization toward normal in a series of patients without organic heart disease, but has little or no effect on T abnormality in patients with organic heart disease. The test has been shown to be safe in the patients for whom it would be useful, but potentially dangerous in patients with documented heart disease. In addition, the dose and mode of administration are critical to the result.

REFERENCES

1. Wasserburger, R. H., and Corliss, R. J.: Value of oral potassium salts in differentiation of functional and organic T wave changes, Am. J. Cardiol. 10:673, 1962.
2. Sharpey-Schafer, E. P.: Potassium effects on T wave inversion in myocardial infarction and preponderance of a ventricle, Brit. H. J. 5:80, 1943.

3. Schlachman M and Rosenberg B The effect of potassium on inverted T waves in organic heart disease, Am. Heart J 40:81 1950.
4. Bryant J M Effect of potassium on the ventricular deflections of the electrocardiogram in hypertensive cardiovascular disease Proc Soc. Exper Biol & Med 67:557 1948.
5. Dodge H T Grant R. P and Seavey P W Effect of induced hyperkalemia on the normal and abnormal electrocardiogram Am Heart J 45 725 1953
6. Viscidi I C and Geiger A J Electrocardiographic observations on 500 unselected young and its t work. Am Heart J 26 763 1943.
7. Graybiel A M Farland R. A. Gates, D C., and Webster F A Analysis of the electrocardiograms obtained from 1000 young healthy aviators, Am. Heart J 27:524 1944
8. Stewart C A and Manning G. W A detailed analysis of the electrocardiograms of 500 RCAF aircrew Am. Heart J 27:502 1944
9. Thomas, C. B The significance of electrocardiographic abnormalities in young adults, Bull. Johns Hopkins Hosp 74:229 1944
10. Averill K H and Lamb L E Electrocardiographic findings in 67,375 asymptomatic subjects I Incidence of abnormalities, Am. J Cardiol 6 76 1960
11. Hiss, R G et al Electrocardiographic findings in 67,375 asymptomatic subjects. VIII Non specific T wave changes Am J Cardiol. 6:178, 1960
12. Sennenbach W Some common conditions not due to primary heart disease that may be associated with changes in the EKG Ann Int. Med. 25:632 1946.
13. Mainzer F and Krause M The influence of fear on the electrocardiogram Brit. Heart J 2:221 1940.
14. Hartwell A. S. Barrett, J B Graybiel A., and White, P D The effect of exercise and of four commonly used drugs on the normal electrocardiogram, with particular reference to T wave changes, J Clin. Invest. 21:409 1942.
15. Loftus, T A., Gold, H and Diethelm, O : Cardiac changes in the presence of intense emotion, Am J Psychiat 101:697 1945
16. Katz, L. N Electrocardiography ed. 2, Philadelphia, 1946 Lea & Febiger Publishers.
17. Wendkos, M H. and Logue R. B. Unstable T-waves in Leads II and III in persons with neuro-circulatory asthenia, Am. Heart J 31 711, 1946.
18. Scherf D and Schlachman M The electrocardiographic changes caused by hyperventilation Am. J M Sc. 213:342, 1947
19. Heyer H. E. Winans, H. M and Plesinger V I Alterations in the form of the electrocardiogram in patients with mental diseases, Am. J M Sc. 214:23 1947
20. Magendantz, H and Shortsleeve, J Electrocardiographic abnormalities in patients exhibiting anxiety Am. Heart J 42:849 1951
21. Blom, G. E. A review of electrocardiographic changes in emotional states, J Nerv & Ment. Dis. 113:283 1951
22. Goldberger E. Unipolar electrocardiography ed. 3 Philadelphia, 1953 Lea & Febiger Publishers, p. 161.
23. Wasserburger R. H T wave and anxiety Heart Bull. 9:54 May June, 1960.
24. Wasserburger R. H : The riddle of the labile T wave, Am J Cardiol. 2:179 1958.
25. Wasserburger R. H. and Lorenz, T H. Effect of hyperventilation and Pro-banthine on isolated RS-T segment and T-wave abnormalities, Am. Heart J 51:666 1956.
26. Wasserburger R. H., Siebecker K. L., J and Lewis, W C. Effect of hyperventilation on the normal adult electrocardiogram, Circulation 13:850 1956.
27. Kiessling C. E., Schaaf R. S and Lyle, A. M A study of T wave changes in the electrocardiograms of normal individuals Am. J. Cardiol. 13:598 1964
28. Mason, J K. Asymptomatic coronary artery disease in young men frequency Brit. M J. 2 1234 1964.
29. Winkler A. W Hoff H. E., and Smith, P K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride, Am J Physiol 124:478, 1938.
30. Brown, H. Tanner G. L., and Hecht, H H The effect of potassium salts in subjects with heart disease, J Lab. & Clin. Med. 37:506, 1951
31. Wendkos, M H The effects of a potassium mixture on abnormal cardiac repolarization in hospitalized psychiatric patients, Am. J. M Sc. 249:412 1965
32. Sleeper J C., and Orgain, E. S. Differentiation of benign from pathologic T waves in the electrocardiogram, Am. J Cardiol. 11:338, 1963
33. Boyadjian, N Dechamps, G and Van Doorn, F Effect of massive ingestion of potassium for the diagnosis of negative T waves, Acta cardiol 13:607 1958.
34. Wasserburger R. H and Alt, W J The normal RS-T segment elevation variant, Am J Cardiol. 8 184 1961
35. Prinzmetal, M et al. Angina pectoris III Demonstration of chemical origin of S-T deviation in classic angina pectoris, its variant form early myocardial infarction, and some noncardiac conditions, Am. J Cardiol. 3:276, 1959
36. Prinzmetal, M et al. Nature of ischemic electrocardiographic patterns in the mammalian ventricles as determined by intra-cellular electrocardiographic and metabolic changes, Am J. Cardiol. 8:493 1961
37. Prinzmetal, M et al.: Angina pectoris VII The nature of S-T depression in acute myocardial ischemia, Am. J Cardiol. 13:498, 1964
38. Prinzmetal, M et al. Angina pectoris IV Clinical and experimental difference between ischemia with S-T elevation and ischemia with S-T depression, Am. J Cardiol. 7:412, 1961.
39. Sodi-Pallares, D : Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction Am. J Cardiol. 9:166, 1962.
40. Sodi-Pallares, D The polarizing treatment of acute myocardial infarction. Possibility of its

se in other cardiovascular conditions, Dis. Chest 43:121, 1963.
41. Harris, A. S., et al.: Excitatory factors in ventricular tachycardia resulting from myocardial ischemia. Potassium major excitant, Science 119:200, 1954.
42. Weidmann, S. Effect of current flow on the membrane potential of cardiac muscle J Physiol 115:227 1951
43. Illes, R G Smith, C B and Lamb, L E Pitfalls i interpreting electrocardiographic changes occurring while monitoring stress procedures, Aero-pace Med 31:9 1960

Unusual QRS complexes produced by pacemaker stimul

With special reference to myocardial tunnelling and coronary sinus stimulation

Agustin Castellanos Jr M D F.A C C
Orlando Maytin M.D
Louis Lemberg M.D F.A C C
Cesar Castillo M.D
Miami Fla

It is generally accepted that pacemaker impulses falling outside the vulnerable period produce a stimulus artifact or spike which is followed by a single ectopic beat. The morphology of the ventricular complexes usually follow the criteria set by Barker and co-workers[1] right ventricular stimulation yields a left bundle branch block (LBBB) pattern whereas left ventricular excitation results in a right bundle branch block (RBBB) contour However exceptions to these postulates are frequent.[2-4] They will be presented hereby since their understanding increases our knowledge of human electrophysiology In addition certain clinical implications can be drawn and used thereafter in the proper management of patients with artificial pacemakers.

Classical pacemaker induced ventricular beats

Endocardial stimulation of the right ventricular apex produces a left bundle branch pattern associated with abnormal left axis deviation (Figs. 1 top left, and 2) The latter is defined according to Grant[5] as an axis between $-30°$ and $-90°$ in the frontal plane. This morphology occurs during transient or permanent transvenous pacing. It is evident that the excitation wave cannot proceed further down so that it propagates in an apex to-base direction throughout the electrically dominant left ventricle. Apical right ventricular pacemakers can thus be induced among the various causes of abnormal left axis deviation[6,7]

An exception to the statements made in the preceding paragraph can be found in a vectorcardiographic study by Zoneraich and associates.[8] These authors observed that the frontal plane maximal QRS vector was deviated superiorly and to the right in some of their patients with apical right ventricular pacemakers. However research performed in our laboratory has explained this paradoxical behavior of excitation. If the horizontal level at which the Frank leads are placed across the chest is too low significantly below the dipole center the Y lead by virtue of this technical artifact, will resemble Y lead a negative QRS complex will be recorded in both

From the section of Cardiology Department of Medicine, University of Miami School of Medicine, the Division of Electrophysiology Jackson Memorial Hospital, and the Veterans Administration Hospital, Miami, Fla.
Received for publication September 11, 1968.

Fig. 1 Types of electrical (QRS) axes produced by different pacemaker sites

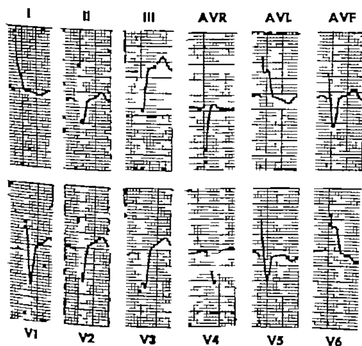


Fig. 2 Left axis deviation resulting from transvenous stimulation of the right ventricular apex.



Fig. 3 *Left* Epicardial stimulation of the right ventricular base producing left bundle branch block pattern with normal axis *Right* Epicardial left ventricular stimulation resulting in a RBBB pattern with right axis deviation

Consequently the maximal vector will appear to be oriented superiorly and to the right in spite of the fact that there is true *left* (rather than right) axis deviation The electrical forces are really oriented toward the lateral region of the left ventricle Such an unusual axis is obviated when the vectorcardiographic electrodes are placed on the fourth intercostal space with the patient supine

Epicardial implantation in the more basal portions of the right ventricle has been proposed by some workers.[9] In these instances the QRS complexes will show a LBBB contour without left axis deviation (Figs. 1 top right and 3 left) because the general sequence of activation occurs in a base to-apex direction The electrical axis points to the left and inferiorly

Pacemakers implanted in the left ventricle with the usual techniques produce QRS complexes with a right bundle branch block morphology [6,7] The electrical axis is oriented to the right and inferiorly and is consistent with the rather superior implantation of the electrodes (Figs. 1 bottom and 3 right) A RBBB pattern is always present in V_1, but not necessarily in V_2 This finding is dependent on the location of the maximal QRS vector in the horizontal plane. An anterior orientation yields a positive deflection in both V_1 and V_2 A slight posterior deviation produces a negative deflection in V_2, but still with an R wave in V_1 Vectorcardiographic studies have revealed that Lead V_1 is not a good lead to differentiate between anterior and posterior forces.[11] However a negativity in all chest leads is exceptional in patients with implanted left ventricular pacemakers, for in such cases the maximal vector would have to be directed to the right and posteriorly This indicates a more anterior than usual implantation in the vicinity of the right ventricle.

An unusual electrocardiogram (ECG) obtained from a patient with a left ventricular pacemaker is presented in Fig. 4 In this case, the electrodes were attached to lowermost (apical) and anterior region of the left ventricle This unit was built in the Soviet Union and implanted in Cuba early in 1967 To our knowledge this is the first report on a Soviet pacemaker appearing in the American literature There is an S_1 S_2, and S_3 pattern in the standard leads because the *QRS* axis points directly toward the right arm. In addition both V_1 and V_6 (as well as the rest of the precordial leads) show predominantly negative deflections. Thus the general sequence of activation occurs in a superior rightward and posterior fashion.

Figs. 1 through 3 show the classical QRS patterns produced by artificial pace

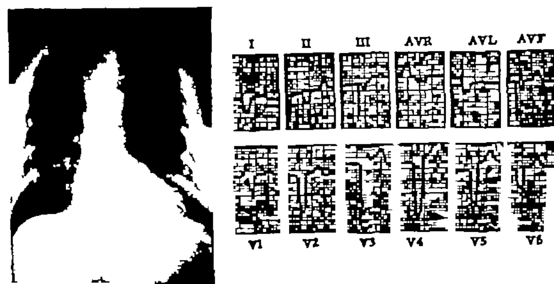


Fig 4 Unusual electrocardiogram produced by pacemaker implanted in the apex of the left ventricle

makers. Deviation from these morphologies is not rare. Unusual QRS complexes produced by pacer stimuli will be presented in the following sections.

Right axis deviation produced by transvenous right ventricular pacemakers

An unusual ECG from a patient with a right ventricular pacemaker was presented in a previous communication from our department (Fig 4 of reference 3) Instead of showing the left bundle branch block morphology characteristic of right ventricular stimulation, there was superior and rightward orientation of the electrical axis. Both V_1 and V had predominant S waves, indicating a right posterior spread of activation in the horizontal plane. In general, this ECG resembled the one shown in Fig. 4 which was produced by an epicardial, apical left ventricular pacemaker In the patient mentioned above, the tip of the catheter was found to be impinged in the right ventricular endocardium one year later when he required a thoracotomy for implantation of a left ventricular pacer Hence it seems that similar QRS patterns can occur after stimulation of the apex of the heart at either side of the interventricular septum.

There are several possibilities by which a transvenous pacer can produce a right bundle block pattern Perforation of the interventricular septum is extremely rare and to our knowledge has not been reported However cases have been described in which perforation occurred in the anterior wall of the right ventricle with extrusion of the catheter and epicardial stimulation of the left ventricle.[11] A similar phenomenon occurred in one of our cases (Fig 5) Immediately after placement of a right ventricular catheter the ECG had all the characteristics attributed to right ventricular apical pacing Intermittent capture with a RBBB contour was noted a few hours later The patient died from cardiac arrest while he was being transferred to the x-ray room for re-evaluation and repositioning to the catheter Necropsy (Fig 5) showed that the catheter had penetrated under the trabeculae cornae at the level of the tricuspid ring and tunneled the free wall of the right ventricle finally emerging at the apex. The tip extruded 2 cm from the myocardium and was bent toward the left, resulting in intermittent epicardial stimulation of the left ventricle.

Mower and associates[4] offered three other explanations for the appearance of a right BBB during transvenous pac For instance, the electroca changes presented in our previous



Fig 5 Myocardial tunneling during permanent transvenous pacing The upper arrow shows the point of entrance of the catheter just below the tricuspid valve. The lower arrow points to the extruded catheter tip which was stimulating intermittently the left ventricular epicardium

(Fig 4 of reference 3) could have resulted from an unusual type of propagation from the site of stimulation The impulse might have entered the right branch, propagated by a retrograde fashion to the A V node to finally descend down through the left branch Since conduction through these structures is silent, the surface ECG would record only the initial activation of the nonspecific left ventricular mass. A left to-right sequence of activation would be expected On the other hand these changes can also be explained on the basis of Sodi-Pallares and Calder's[12] concepts of septal anatomy and activation These authors suggested that some portions of the anatomical left septum extended up to the right ventricular endocardium In fact, intracavitary right ventricular potentials recorded from these areas resembled those obtained from within the left ventricle Moreover stimulating these same portions of the septum can be expected to yield QRS morphologies similar to those observed after initial left ventricular excitation

Finally right axis deviation during transvenous pacing can occur if the catheter penetrates into the coronary sinus and stimulates the left ventricle from this unusual position

Transvenous stimulation of the left ventricle via the coronary sinus and its branches

In a patient with complete A V block the catheter penetrated deeply into the coronary sinus. The posterobasal aspect of the left ventricle was stimulated Ventricular capture required 20 volts, whereas a few minutes later the right ventricular endocardial threshold was only 2 volts. It is evident that different QRS patterns can be obtained by pacing the posterior surface of the heart. If the catheter had been introduced into the great cardiac vein it could have activated the lateral rather than the posterobasal portions of the left ventricle. The diagram indicates that activation proceeded from base to apex, resulting in an inferiorly oriented QRS axis. The latter was also directed slightly to the left and of course anteriorly because the site of pacing was posteriorly close to the interventricular groove. Had the catheter been pushed further it is possible that right axis deviation could have occurred as suggested by Mower and associates.[4] The orientation of the maximal QRS vector in the horizontal plane was such that it resulted in a positive deflection in both right and left precordial leads. This pattern resembled bilateral bundle branch block since the intrinsicoid deflection was delayed in V_1 and V_6.[11] It was also similar to the spatial orientation seen in Wolff Parkinson White type A.[12] In fact, Sodi-Pallares and Calder[12] have suggested that the latter could well be due to the initial pre-excitation of the posterior surface of the left ventricle.[12]

Other types of left ventricular stimulations during transvenous pacing are seen whenever the catheter tip penetrates deeply into the coronary sinus (see below)

The patient shown in Figs. 7 and 8 had a bipolar transvenous permanent catheter (guided with metallic stylets) inserted early in 1966. The tip was advanced to the right ventricular apex and impinged in

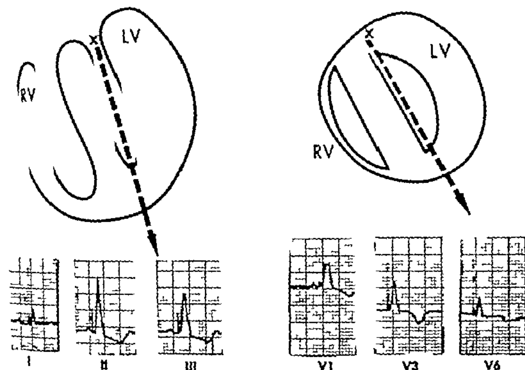


Fig 6. Left ventricular stimulation through the coronary sinus during transient transvenous pacing. Note the lateral bundle branch block pattern with normal axis

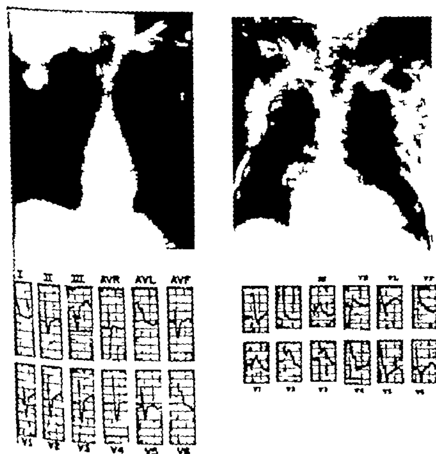


Fig 7 Stimulation of the right ventricular apex (left). Epicardial stimulation of the left ventricle ... the catheter penetrated into the coronary sinus and its branches (right).



Fig 8 (Same case as in Fig 7) Arrows 1 and 3 point t the superior vena cava. Arrow 2 indicates the position of the catheter inside the posterior vein of the left ventricle after opening the latter Penetration of the catheter in this vein is indicated by arrow 4 A left lateral view of the heart is show t the left and posteroperio view t the right PIS Posterior interventricular sulcus.

the endocardium from which all spikes captured the ventricles.

The guiding stylet was left in place to achieve better anchoring of the catheter electrode. A Medtronic fixed rate pacemaker was implanted in the right subclavicular area. The catheter tip appeared to be at the apex of the right ventricle (Fig 7 left) The ECG showed continuous pacing at a rate of 71 The QRS complexes following every spike had a left bundle branch block pattern as expected Stimulus intensity was two times the diastolic threshold Shortly after implantation the pacemaker failed to capture the ventricles. Instead intermittent diaphragmatic pacing was noticed. The patient did not complain of pain No rubs or signs of tamponade were present A few hours later diaphragmatic pacing ceased and the ECG showed the pattern of right bundle branch block with continuous ventricular capture (Fig 7 bottom right) A second x ray showed the catheter tip well over left ventricular area (Fig 7 upper right) There had been no change in stimuli intensity Our first impression was that the interventricular septum had been perforated. This extremely rare complication was attributed to the fact that the guiding stylet had been left in place The patient remained well for 18 months, at which time he died after being in a coma for three days Death was attributed to cerebral hemorrhage.

The necropsy (Fig 8) showed that the catheter had not perforated the intraventricular septum as was previously assumed. On the contrary it had become dislodged from the right ventricular apex and had entered the coronary sinus. The tip was introduced into the posterior vein of the left ventricle advancing at a distance of about 4 inches within the coronary vein system From this position it had been stimulating continuously the epicardial portions of the lateral wall of the left ventricle for a year and a half

Abrupt changes in QRS morphology of a right ventricular endocardial pacemaker without dislodgement of the catheter tip

Atriosynchronized pacemakers usually are implanted in the left ventricle Therefore they produce a RBBB pattern. Occasionally atriosynchronization is performed transvenously using two catheters. One, in the right atrium picks up the P wave and delivers it to the pacemaker

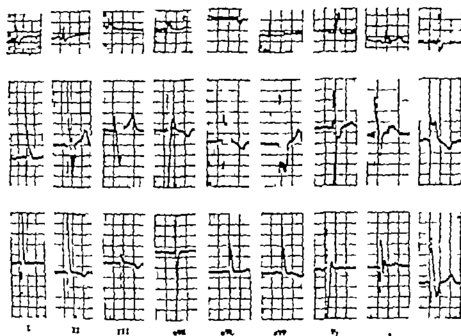


Fig. 9. Changes in the morphology of the QRS complexes occurring in a patient with a transvenous triggered pacemaker. The top strip was recorded during normal atrioventricular conduction. In the middle strip, the ventricles are activated only by the pacemaker. At this moment conduction was not occurring through the anatomical A-V junction. Finally, the lower strip shows a change in QRS morphology resulting from the simultaneous depolarization of the ventricles by the supraventricular impulse and the artificial pacemaker.

The latter in turn depolarizes the ventricle through the second, the right ventricular catheter. In these cases the corresponding QRS complexes show a LBBB morphology. A characteristic feature of synchronized pacemakers is that the QRS complexes triggered by the P waves and those appearing during their escape periods have a similar morphology. This is understandable since in both cases the spike is responsible for depolarizing ventricles in their totality. A change of QRS morphology after periods of normal atrio-synchronization therefore suggests that the catheter tip was not in its original position. The following case is an exception to the rule.

The top row of Fig. 9 shows RBBB, sinus rhythm, and a P-R interval of 0.16 sec. The patient then developed an intermittent complete A-V block which required an electronic pacemaker. The middle row was obtained during permanent, transvenous atriosynchronization. There are large spikes in all leads preceding the wider QRS complexes. Abnormal left axis deviation (close to $-60°$) is present in the standard leads. There is a small negative deflection in V_1 and a predominant R wave in V_6. The spatial orientation of the ventricular complexes is characteristic of the one produced by right ventricular apical pacemakers (Figs. 1, upper left, and 2). Vectorial analysis proves that stimulation of the ventricles was performed in its totality by the pacemaker. This impression was confirmed by carotid sinus pressure (not shown). The maneuver slowed the sinus node. Pacemaker escapes appeared. The resulting QRS complexes were identical to the ones triggered by the P waves.

Unexpected findings were seen in the bottom row. They initially suggested a change in location of the catheter tip. Although the spatial orientation of the spikes is the same, it is interesting to note that the resultant QRS complexes are different from those in the middle row. For instance, the electrical axis in the standard leads now points toward $+30°$. There is a predominant S wave in V_6. The most significant deflection in V_1 is a small R wave. A careful analysis of the QRS patterns

Vektorkardiographische Untersuch ng des Hergens fei implantertem Schrittmacher Gesell. fur Kreislauff 30:239 1964
12. Sodi-Pallares, D nd Calder R M New bases of lectrocardiography St. Louis 1956 The C V Mosby Company
13 Danielson G K. Shabetai, R and Bryant, L. R Failure of endocardial pacemaker due to myocardial perforation, J Thoracic & Cardiovas Surg 51:42 1967
14 Segers, M and Enderle, J Les blocs intraventriculaires bilatéraux Acta cardiol. 6 1015 1951
15 Castellanos, A. J Lemberg, L., and Gosselin, A. Double artificial ventricular parasystole, Cardiologia 47:273 1965.
16. Gerbaux, A. and Lenègre, J Observations sur rythmes à double commande (normale et par électrostim lation) constatés après implantation d stimulateur i terne pour maladie d Adams-Stokes, Arch. mal coeur 57:286, 1964.
17 Furman, S. and Robinson, G. Use of intracardiac pacemaker in correction of total heart blocks, S. Forum 9:245 1958.

Congenital mitral valve disease associated with coarctation of the aorta

A report of 39 cases

R. N. Easthope, M.B., M.R.A.C.P.
Ray L. Tawes, Jr., B.A., M.D.
R. E. Bonham Carter, M.A., M.B., F.R.C.P.
Eoin Aberdeen, M.B., B.S., F.R.C.S., D.C.H.
D. J. Waterston, M.B.E., F.R.C.S.
London, England

Congenital mitral valve disease as an isolated lesion is a rare anomaly. Most reported experience has been with relatively few cases associated with other congenital cardiac defects.[1-3] Mitral stenosis occurs with increased frequency in patent ductus arteriosus, aortic stenosis, ventricular septal defect and occasionally with atrial septal defect (Lutembacher's syndrome) and endocardial fibroelastosis. Mitral regurgitation (incompetence) is commonly associated with endocardial cushion defects (ostium primum atrial septal defects or complete atrioventricular canal) and occasionally with endocardial fibroelastosis. There are few reported cases of congenital mitral valve defects associated with coarctation of the thoracic aorta.[4-10] This paper draws attention to this relationship and its influence on survival.

Methods

Mitral valve defects were documented by either cardiac investigation (i.e., cardiac catheterization and selective angiocardiography), operation, or postmortem examination. Cases diagnosed clinically but without confirmation by one of the above methods were excluded, as were those children with any evidence suggestive of rheumatic fever or of subacute bacterial endocarditis. Children with endocardial cushion defects were excluded since a cleft anterior (septal) leaflet of the mitral valve is an integral part of this complex defect. Patients with the hypoplastic left heart syndrome were also excluded.[11]

Two sources of patient material were available. We have reviewed the 15 year operative experience from 1953 to 1967 with 333 children (179 being under one year of age) who had operations for coarctation of the thoracic aorta and we assessed the coincidence of mitral valve defects (Group I). The second source was a separate group of 74 children coming to postmortem examination during the same period who had coarctation of the aorta as part of a complex of congenital cardiac

From the Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London, England.
This study was supported by the British Heart Foundation.
Received for publication Sept. 17, 1968.
*Present address: Cardiac Department, The Hospital of Sick Children, Toronto, Ontario, Canada.
**Giannini Foundation Fellow, Department of Surgery, University of California Medical Center, S.F.

Table I. Clinical data and method of diagnosis in patients undergoing coarctation resection (Group I)

Case No.	Patient, sex	Age at diagnosis (Coarct.)	Age at operation (Coarct.)	C.C.F.	P.H.T.	Type of coarct.	Mitral valve lesion	Other cardiac lesion	Method of diagnosis of mitral valve disease			Outcome
									Cardiac investigation	Operation	Autopsy	
1	C. D., M	1 mo.	2 mo.	+	0	Juxtalig	MR MS	0	+	−	−	Alive and symptom-free; increasing LVH on ECG; awaiting reinvestigation
2	P. S., M	6 wk.	3 yr	+	+	Juxtalig	MS	0	+	+	−	Open mitral valvotomy at 3½ years relieved C.C.F. refractory to medical treatment
3	S. M., F	6 mo.	4 yr	+	+	Postlig	MR	0	+	−	−	Alive and well, on digitalis; awaiting mitral annuloplasty
4	R. W., M	2 yr	2½ yr	+	+	Juxtalig	MR	AS	+	−	−	Alive; C.C.F. improved on maintenance digitalis
5	M. F., M	1 mo.	5 yr	+	0	Juxtalig	MR	0	+	−	−	Alive and well; not in C.C.F. on digitalis
6	D. H., F	3 mo.	7½ yr	0	+	Preductal	MR	PDA	+	−	−	Alive and well; moderate LVH on ECG
7	T. J., M	12 yr	12 yr	0	+	Juxtaductal	MS	PDA	+	−	−	Alive and well
8	S. E., M	3 wk.	5 wk.	+	+	Preductal	MR	PDA, VSD	+	−	−	Alive and well; recoarctation resected at 6½ years
9	L. L., F	5 wk.	12 wk.	+	+	Juxtaductal	MR	PDA, VSD	+	−	−	Alive; recoarctation awaiting resection
10	S. N., M	1 wk.	3 mo.	+	+	Juxtaductal	MR	0	+	−	−	Alive; frequent respiratory infections; awaiting mitral valve repair
11	P. B., M	9 yr	9 yr	0	+	Juxtaductal	MR	PDA	+	+	−	Alive; mitral valvotomy at 12 years, 3 to 4 mm. orifice opened fully ? abnormal chordae
12	M. B., M	2 yr	2½ yr	0	+	Postductal	MR MS	PDA	+	−	−	Alive and well; LVH + on ECG
13	J. W., M	1 yr	2 yr	+	+	Juxtaductal	MR	PDA	+	−	−	Alive; recoarctation resected at 14 years
14	E. H., F	5½ yr	5½ yr	0	?	Preductal	MR MS	PDA, VSD	−	−	+	D.O.T. PA hemorrhage, VF
15	N. M., F	2 mo.	11 mo.	+	0	Juxtalig	MS	EFE, LA	−	−	+	D.O.T.; VF
16	A. F., F	6 wk.	2 mo.	+	?	Juxtalig	MR	EFE, LV Subaortic stenosis, Abl. TR	−	−	+	D.O.T.; VF

C						Preductal	Pre- mesa	Mus. vul. vsd	—	—	+	Died C.C. [illegible] postoperatively in [illegible] pulmonary compli cations
19	J S	M	6 wk.	3 mo.	+	?	Preductal	MS	PDA, VSD TR	—	—	+	Died 8 days postoperatively in C.C.F with pulmonary compli cations
20	L. D	F	2 mo.	9 wk.	+	+	Preductal	MR MS	PDA, VSD x 2	—	—	+	Died 12 days postoperatively in C.C.F with pulmonary compli-cations
21	M F	M	5 wk.	6 wk.	+	0	Preductal	MR	PDA, EFE, LV	—	+	+	Died 36 hours after mitral annulo-plasty (8 months after resection of coarct.)
22	D K	M	2 wk.	4 wk.	+	+	Preductal	MR	PDA, AS	+	—	—	Late death, 7 month postoperatively; ? cause of death
23	B G	M	1 wk.	3 wk.	+	+	Preductal	MR	PDA	+	—	+	Died 4 hours after resection in C.C.F with pulmonary com plications

Abbreviations: Coarct., Coarctation of aorta; C.F., congestive cardiac failure; P.H.T., pulmonary hypertension; Juxtalig., juxtaligamental; Postlig., postligamental; MR, mitral regurgitation; MS, mitral stenosis; AS, aortic stenosis; PDA, patent ductus arteriosus; VSD, ventricular septal def[illegible]; EFE, endocardial fibroelastosis; LA, left atrium; LV, left ventricle; ASD, atrial septal defect; TR, tricuspid regurgitation; LVH, left ventricular hypertrophy; [illegible], death on operating table; VF, ventricular fibrillation; PA, pulmonary artery.

lesions but who had not had resection of the coarctation. The incidence of mitral valve defects was determined in this group (Group II)

Results

Group I Coarctation resected

CLINICAL DATA AND METHOD OF DIAGNOSIS (TABLE I) Mitral valve defects occurred in 23 of 333 patients in the operative group an incidence of 7 per cent Sixteen were male and 7 were female The age at diagnosis ranged from one week to 12 years with a median of 6 weeks All but one patient presented with hypertension in the arms and absent or weak femoral pulses. (Patient No. 17 with a preductal coarctation had forceful femoral pulses) Mitral valve disease was suspected preoperatively in only 14 cases (61 per cent)

Congestive cardiac failure was present in 78 per cent (18 of 23) at the time of resection of the coarctation. All of the infants were in congestive cardiac failure at the time of operation The failure was refractory to medical therapy in 12 patients and the coarctation was resected as an emergency procedure.

Mitral regurgitation was present in 13 children mitral stenosis in 5 and 4 had a combined lesion. One child had mitral atresia

Associated cardiac lesions were common A patent ductus arteriosus was present in 16 children In 10 children the patent ductus arteriosus was associated with a preductal coarctation (Table I) Cardiac lesions other than mitral occurred in 11 children (47 per cent) ventricular septal defect being the most common.

HEMODYNAMIC FINDINGS (TABLE II) Nineteen of the 23 patients in the group undergoing coarctation resection had cardiac catheterization. Eleven were investigated before resection of their coarctation 7 after and 1 patient both before and after resection.

The left ventricle was catheterized in 10 patients, and the left atrium in only 4 However a satisfactory pulmonary arterial wedge pressure was obtained in 14 Fourteen patients had pulmonary hypertension (pulmonary artery systolic pressure > 40 mm. Hg) and 13 had elevat of the pulmonary wedge pressure.

Table II Hemodynamic and angiocardiographic findings in Group I patients

Case No	Age (yr)	Before part. resected	After resection	Pressures (mm Hg)						Angiocardiogram	
				P A	P A wedge	L A	L V	[illegible]	Desc or F A	L V	Other
1	2/12	+		90/10 $\overline{17}$	m v = 16	—	—		70 50		Large L A slow to empty (P A angio)
	/12	+		50/12 $\overline{25}$	7	—	—				—
	2 11/12	+		70/30 $\overline{45}$	18	—	—	R B A 130/70 = 80	45 90/60 70	—	—
	3	+		76/40 $\overline{50}$	—	—	85/9 12	90/48 60	70/50 55	Small mitral orifice (negative jet) restricted cusp movement	—
3	3 11/12	+		52/25 $\overline{40}$	$\overline{30}$	—	110/14 24	110/60 $\overline{80}$	—	M R ++ large L A	Fig 3
4	2 6/12	+		70/34 $\overline{46}$	$\overline{20}$	a 25 v 30 $\overline{28}$	90 11 20	95/55 $\overline{70}$	62/42 $\overline{52}$	M R ++ large L A	—
	2 8/12		+	60/30 $\overline{40}$	—	a 26 v 30 $\overline{20}$	108/8, 25	90/55 $\overline{70}$	95/60 76	M R ++ large L A	Fig 2
5	5 1/12	+		35/13 $\overline{19}$	a 20 v 22 $\overline{15}$	—	140/3, 10	140/68 $\overline{90}$	78/38 $\overline{68}$	M R +	—
6	6 8/12	+		85/55 $\overline{67}$	—	—	—	—	95/60		—
	6 10/12	+		—	—	—	105/10, 13	105/70	90/60	M R + —	—
7	12	+		60/25	a 40 v 26 $\overline{25}$	—	—	R B A = 160/70	70/60	—	—
8	6 3/12		+	40/15 $\overline{25}$	13 v 19 $\overline{16}$	—	135/8, 15	130/80	95/80	M R + V S D	Recoarctation
9	6		+	42/15 25	18 v 29 $\overline{18}$	—	1 0/5, 20	120/70 95	80/70	M R + V S D	Recoarctation
10	2 5/12		+	46/15 30	a 15 v 18 $\overline{13}$	—	—	—	—	—	—
	2 5/12		+	—	—	22 v 25 $\overline{20}$	100/0 20	100/60	85/60	M R +++	—
	3 10/12		+	60/40 $\overline{30}$	21 v 27 $\overline{21}$	—	110/0 14	110/78 $\overline{90}$	100/85	M R +++ Fig 1 large L A	Recoarctation

			+	[illegible]	[illegible]	—	—	n A — 4/30	—	—	—
2	3 4/12	+		70/30 $\overline{4}$	$\frac{2}{20}$ $\overline{2}$	—	—	—	80/60	—	—
13	13		+	65/20 $\overline{37}$	28 v 24 $\overline{22}$	—	180/0 16	180/110 $\overline{180}$	120/98 $\overline{105}$	M R ++	Recoarctation
15	11/12	+		25/8	—	—	—	—	—	—	—
17	5/52	+		40/25	—	4 v 7 4	—	—	40/25	—	—
20	1/12	+		100/45 $\overline{55}$	—	—	—	—	75/45 $\overline{55}$	—	—
21	2/12		+	30/15	10 v 12 9	—	—	—	75/40	—	—
—	8 12		+	40/25 $\overline{25}$	—	—	—	—	—	—	L.A. slow to empty; L.A. angio.
23	1 5	+		85/50 $\overline{65}$	—	17 28 $\overline{18}$	125/10, 20	—	68/42 $\overline{55}$	—	—

$\overline{m}$, Mean pressure. M R, Mitral regurgitation. + mild ++ moderate +++ severe

of the patients were in cardiac failure and therefore an elevated pulmonary arterial wedge pressure was not by itself an indication of mitral valve disease.)

ANGIOCARDIOGRAPHIC FINDINGS (TABLE II) Clear angiocardiographic evidence of mitral regurgitation was obtained in 10 patients. Examples are shown (Figs. 1 2 and 3) One patient (No 2) had evidence of mitral stenosis. Two others (Nos. 1 and 22) had indirect evidence of mitral stenosis angiographically but had good clinical electrocardiographic, and radiographic evidence of this lesion

OPERATIVE RESULTS (TABLE I)

1 Hospital deaths Eight (39 per cent) of the 23 children died in hospital following resection of their coarctation (Fig 4) Seven of the deaths occurred in infants 5 being under 3 months of age. Four died at operation with ventricular fibrillation Four died within 2 weeks of resection in persistent congestive failure with pulmonary complications.

2. Late deaths One death occurred 7 months after coarctation resection from an unknown cause. The other late death occurred 36 hours after mitral annuloplasty performed 8 months after resection of the child s coarctation.

3 Survivors There are 13 children now living The median age at the time of resection was 2½ years compared to a median of 2 months for those who died The survivors have been followed for periods of 7 months to 11½ years (mean 4 years 7 months)

Two children have had successful mitral valvotomies. One has been followed for 8 years after a closed mitral valvotomy and is well without evidence of mitral regurgitation The other had a limited mitral valvotomy under cardiopulmonary bypass of a parachute type of mitral valve with relief of persistent congestive cardiac failure 6 months after resection of his coarctation He is well 4 months postoperatively Two children with mitral regurgitation are awaiting mitral valve repair Three others have had a recoarctation successfully resected

The 6 remaining children are doing well but will probably require mitral valve surgery (valvotomy repair or replacement) in the future



Fig. 1 Case 10 LV angiocardiogram anteroposterior projection. Severe mitral regurgitation; recoarctation of aorta. *A* Systole. *B* Diastole.



Fig. 2 Case 4 LV angiocardiogram, anteroposterior projection. Severe mitral regurgitation coarctation aorta resected. *A* Systole. *B* Diastole.

POSTMORTEM FINDINGS (TABLE III) Of the 9 children in the operative group coming to postmortem examination 4 had mitral stenosis, 4 had incompetent mitral valves and one had mitral atresia. Six had endocardial fibroelastosis involving the left atrium and/or left ventricle. In 6 of the 9 children a cardiac anomaly in addition to coarctation of the aorta, patent ductus arteriosus, and mitral valve disease was present this being a ventricular septal defect in 4.



Fig. 1. Case 1. LV angiocardiogram, anteroposterior projection. Severe mitral regurgitation, coarctation of aorta.

Group II. Coarctation not resected

CLINICAL DATA (TABLE IV). Mitral valve defects occurred in 16 of 74 children, an incidence of 22 per cent. These children did not have resection of their coarctation and postmortem examination confirmed or revealed the associated defects. The age at death of these 16 children ranged from 1 day to 4 years (median 7½ months). Twelve were infants and 6 were under 3 months of age.

The nature of the terminal illness is summarized in Table IV. Most children died before the diagnosis was established or while awaiting surgery for the coarctation. Ten children (63 per cent) died within 48 hours of admission to hospital. Earlier in the series, two children died during aortic valvotomy with ventricular fibrillation. Coarctation was not suspected preoperatively as both had palpable femoral pulses associated with a preductal coarctation. One other child died 2 days after ligation of a patent ductus arteriosus. One

Table III. Postmortem data in Group I patients (coarctation resected)

Case No.	Mitral valve at postmortem	Type of coarctation	Other cardiac anomalies
14	Dilated ring, thickened free edges of cusps	Preductal	Patent ductus arteriosus, small membranous ventricular septal defect, dilated tricuspid valve ring, endocardial fibroelastosis of left atrium
15	Mitral stenosis	Juxtaligamental	Endocardial fibroelastosis of left atrium
16	Shortened chordae, valve obviously incompetent	Juxtaligamental	Secundum atrial septal defect, subaortic stenosis (muscular); endocardial fibroelastosis of left ventricle; dilated tricuspid valve ring, persistent (left) S.V.C. → coronary sinus → R.A.
17	Mitral stenosis	Preductal	Aortic valve atresia, patent ductus arteriosus, endocardial fibroelastosis of left atrium and left ventricle
18	Mitral valve atresia	Preductal	Patent ductus arteriosus, ventricular septal defect (membranous), quadricuspid pulmonary valve
19	Mitral stenosis; shortened chordae	Preductal	Small membranous ventricular septal defect, patent ductus arteriosus, tricuspid septal cusp anomaly
20	Mitral stenosis, 0.5 cm. diam. orifice, shortened chordae attached to single papillary muscle	Preductal	Patent ductus arteriosus, persistent (L) S.V.C. → coronary sinus → R.A., bicuspid aortic valve, membranous ventricular septal defect, muscular ventricular septal defect, endocardial fibroelastosis of left atrium
21	Tethered, thickened chordae; valve obviously incompetent	Preductal	Patent ductus arteriosus, endocardial fibroelastosis of left ventricle
22	Dilated ring; shortened chordae; deficient posterior cusp	Preductal	Patent ductus arteriosus

Table IV Postmortem findings in Group II patients (coarctation not resected)

Case No.	Sex	Age at death	Nature of terminal illness	Mitral valve	Type of coarctation	Associated cardiac anomalies
24	M	9 mo.	Death 24 hr after admission, congestive cardiac failure	Mitral stenosis—thickened, rigid cusps, thickened short chordae	Juxtaligamental	Endocardial fibroelastosis of left auricle and left ventricle
25	M	7 mo.	Death 24 hr after admission, acute bronchiolitis	Mitral stenosis—thickened cusps, partially fused	Preductal	Patent ductus arteriosus, endocardial fibroelastosis of left auricle and left ventricle
26	M	3 yr	Death during aortic valvotomy (ventricular fibrillation)	Mitral regurgitation—dilated ring, short chordae, abnormal cusps (cartilaginous)	Preductal	Patent ductus arteriosus, ventricular septal defect (membranous); bicuspid (stenosed) aortic valve; subaortic stenosis (muscular)
27	F	2 yr	Death 2 days after admission, congestive cardiac failure and bronchopneumonia	Mitral regurgitation—dilated ring, short chordae, rigid anterior cusp, thickened with cartilage	Preligamental	Endocardial fibroelastosis of left auricle and left ventricle, bicuspid aortic valve
28	M	5 days	Death 2 days after division of tracheo-esophageal fistula and gastrostomy for esophageal atresia	Mitral atresia	Preductal	Patent ductus arteriosus, ventricular septal defect (large, membranous); persistent left superior vena cava → coronary sinus
29	F	4 yr	Death 10 hr after admission, myocardial infarction	Mitral regurgitation—taut, shortened chordae, thickened cusps	Preligamental	Aortic stenosis (bicuspid valve); ventricular septal defect (membranous; occluded by adherent cusp of tricuspid valve); thrombosis left coronary artery
30	F	8 mo.	Death during aortic valvotomy (ventricular fibrillation)	Mitral stenosis—narrow ring, diam. 1.2 cm.	Preductal	Patent ductus arteriosus; bicuspid aortic valve (stenosed); subaortic stenosis (muscular)
31	M	3 mo.	Death 2 days after ligation of patent ductus arteriosus (coarctation not resected)	Mitral regurgitation—dilated ring, gelatinous vegetations on cusps	Juxtaductal	Patent ductus arteriosus (ligated); ventricular septal defect (membranous)
32	F	1 yr	Death 2 days after admission, congestive cardiac failure and bronchopneumonia	Mitral regurgitation—dilated ring; absence of chordae; cartilaginous nodules on cusps	Preductal	Patent ductus arteriosus, ventricular septal defect (muscular); dilated tricuspid ring, cartilaginous cusps
33	F	10 days	Death 24 hr after admission, congestive cardiac failure	Mitral regurgitation—very dilated ring; two main cusps and additional frills	Complete aortic arch atresia	Patent ductus arteriosus; tricuspid atresia; ventricular septal defect (membranous); transposition of the great arteries
34	F	8 mo.	Death 2 weeks after admission, congestive cardiac failure and bronchopneumonia	Mitral regurgitation—dilated ring; gelatinous vegetations on cusps	Preductal	Patent ductus arteriosus, persistent left superior vena cava → coronary sinus
35	M	6 wk.	Death 2 days after admission, congestive cardiac failure	Mitral regurgitation—extremely short chordae and papillary muscles	Preductal	Patent ductus arteriosus
36	M	2 wk.	Death 24 hr after admission, congestive cardiac failure	Mitral regurgitation—short, taut chordae	Preductal	Patent ductus arteriosus
37	M	8 days	Death 14 hr after admission, congestive cardiac failure	Mitral atresia	Preductal	Patent ductus arteriosus; ventricular septal defect (large, membranous); tricuspid valve cusps thickened and short chordae

Table IV—Cont'd

Case No.	Sex	Age at death	Nature of terminal illness	Mitral valve	Type of coarctation	Associated cardiac anomalies
[illegible]	F	1 day	Death 12 hr after admission; congestive cardiac failure	Mitral atresia	Preductal	Patent ductus arteriosus, right pulmonary veins → coronary sinus, bicuspid aortic valve; bicuspid right-sided atrioventricular valve
[illegible]	M	7½ mo.	Death (ventricular fibrillation) after test injection of contrast material into left ventricle	Mitral regurgitation—thickened cusps and short chordae	Preligamental	Endocardial fibroelastosis of left auricle and left ventricle; fibrous nodules on tricuspid valve cusps

patient died following myocardial infarction.

POSTMORTEM FINDINGS (TABLE IV). In the second group, the coarctation was preductal in 10 children and in 2 others, preligamental. A patent ductus arteriosus was present in 2 others, one of whom had aortic atresia.

Ten had mitral incompetence (regurgitation), 3 had mitral stenosis, and 3 mitral atresia. All 16 children in this postmortem group had additional cardiac anomalies. Ventricular septal defect occurred in half the cases.

Discussion

It is clear from this study that the association of congenital mitral valve disease with coarctation of the aorta is not rare. The incidence was 7 per cent in the operative group of 333 children. It would be 10 per cent if 12 other children in this group who have only clinical evidence of mitral valve disease were included. The incidence was 22 per cent in a postmortem group of 73 patients who did not have resection of the coarctation.

In most large published series of coarctation of the aorta, mitral valve disease is infrequently mentioned.[13-14] Michaëlsson,[8] reviewing the experience of the University Hospital, Uppsala, Sweden, from 1951 to 1967, found 111 cases of coarctation of the aorta, 11 of whom had congenital mitral valve disease, an incidence of 10 per cent. Bernhard and Norman[15] noted 3 cases of mitral incompetence among 32 infants with coarctation.

On the other hand, most reports of congenital mitral valve disease in the literature contain a significant proportion of patients with associated coarctation of the aorta.[1] There were 23 cases of coarctation in Van der Horst and Hastreiter's[2] comprehensive review of 122 cases of congenital mitral stenosis, an incidence of 19 per cent.

Forty per cent of children with untreated congenital heart disease die in the first year of life.[11,22] Infants with severe multiple cardiac lesions usually develop congestive cardiac failure and die. Early death also occurs with coarctation of the aorta associated with mitral valve disease. We have found that mitral valve disease is present in a significantly greater number of children who die before their coarctation can be resected than in those who come to resection (22 per cent versus 7 per cent). We feel that this explains the apparent discrepancy between the incidence of mitral valve disease in our experience of coarctation of the aorta, and that in previous reports, because a relatively greater proportion of infants is seen at this hospital.

Only by effective diagnosis and therapy will many of these infants survive. Resection of the coarctation as an emergency procedure may be lifesaving, often in the presence of other cardiac anomalies, which may then be correctable later. About half of the infants in persistent congestive cardiac failure can be saved by operation.[22] Most die in early i[illegible] whether or not mitral valve di[illegible] present (Figs. 4 and 5).

The [illegible]gnosis for these chil[illegible]

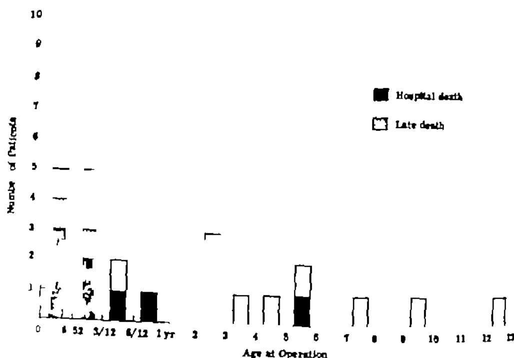


Fig 4 C f the orta with mitral valv disease deaths.

Deaths

Number of Patients

Age at Operation

Fig 5 Coarctation of aorta in 333 patient (1953 t 1967) hospital deaths.

mitral valve disease who survive resection of their coarctation is not good. Van der Horst reported that 20 per cent of children with congenital mitral stenosis die in the neonatal period, 50 per cent within the first year, and only 20 per cent live to 3 years of age. Mitral valvotomy for congenital mitral stenosis has a mortality rate of 40 per cent to 63 per cent and postoperatively mitral regurgitation is common because the valve tissue is so abnormal.[3,21]

The operative results are somewhat more encouraging with congenital mitral incompetence, but depend on the type of abnormality—i.e. dilated mitral valve ring, cleft leaflet, fenestration or ruptured chordae.[1,10-12]

There is a general reluctance to replace the mitral valve with a prosthesis in a child because of 3 principal considerations: growth, thromboembolism and durability of the valve. However Tank and associates[19] recently reported that valve replacement proved the only successful form of treatment in their experience with 14 children 1 to 15 years old with congenital mitral stenosis. Bloodwell and associates[20] recently reported a 28 per cent cumulative mortality rate for 18 mitral valve replacements in children. Long-term results following mitral valve replacement are not yet available.

Summary

Congenital mitral valve defects occurred in 23 (7 per cent) of 333 infants and children who had a coarctation of the aorta resected. A 22 per cent incidence was found at postmortem examination in a separate group of 74 patients who had not had operation for coarctation. Reasons for the relatively high incidence of this combination of cardiac anomalies, previously considered rare, are discussed with special reference to natural selection. The prognosis of those infants and children surviving resection of the coarctation is poor.

REFERENCES

1. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart disease in infancy and childhood, ed. 2, New York, 1967, The Macmillan Company, chap. 37, p. 833.
2. Nadas, A. S.: Pediatric cardiology, ed. 2, Philadelphia, 1963, W. B. Saunders Company, chap. 16, p. 387.
3. Van der Horst, R. L., and Hastreiter, A. R.: Congenital mitral stenosis, Am. J. Cardiol. 20:773, 1967.
4. Ferencz, C., Johnson, A. L., and Wiglesworth, F. W.: Congenital mitral stenosis, Circulation 9:161, 1954.
5. Swan, H., Trapnell, J. M., and Denst, J.: Congenital mitral stenosis and systemic right ventricle with associated pulmonary vascular changes frustrating surgical repair of patent ductus arteriosus and coarctation of the aorta, Am. Heart J. 38:914, 1949.
6. Tsuji, H. K., Shapiro, M., Redington, J. V., and Kay, J. K.: Congenital mitral stenosis, J. Thoracic & Cardiovas. Surg. 53:850, 1967.
7. Monroe, C. A., Milna, G. E., and Orgain, E. S.: Congenital mitral stenosis associated with coarctation of the aorta, bicuspid aortic valve, hypoplasia of the left ventricle, auricular septal defect, and tricuspid valvular malformation, Am. Heart J. 55:343, 1958.
8. Talner, N. S., Stern, A. M., and Sloan, H. E.: Congenital mitral insufficiency, Circulation 23:339, 1961.
9. Daoud, G., Kaplan, S., Perrin, E. V., Dorst, J. P., and Edwards, F. K.: Congenital mitral stenosis, Circulation 27:185, 1963.
10. Elliott, L. P., Anderson, R. C., Amplatz, K., Lillehei, C. W., and Edwards, J. E.: Congenital mitral stenosis, Pediatrics 30:552, 1962.
11. Auger, P., and Wigle, E. D.: Coarctation of the aorta associated with severe mitral insufficiency, Am. J. Cardiol. 21:190, 1968.
12. Sinha, S. N., Rusnak, S. L., Sommers, H. M., Cole, R. B., Muster, A. J., and Paul, M. H.: Hypoplastic left ventricle syndrome. Analysis of thirty autopsy cases in infants with surgical considerations, Am. J. Cardiol. 21:166, 1968.
13. Schuster, S. R., and Gross, R. E.: Surgery for coarctation of the aorta: review of 500 cases, J. Thoracic & Cardiovas. Surg. 43:54, 1962.
14. Glass, I. H., Mustard, W. T., and Keith, J. D.: Coarctation of the aorta in infants: review of 12 years experience, Pediatrics 26:109, 1960.
15. Hamilton, W. F., and Abbott, M. E.: Coarctation of the aorta of the adult type, Am. Heart J. 3:381, 1928.
16. Hallman, G. L., Yashar, J. J., Bloodwell, R. D., and Cooley, D. A.: Surgical correction of coarctation of the aorta in the first year of life, Ann. Thoracic Surg. 4:106, 1967.
17. Mortensen, J. D., Cutler, P. R., Rumel, W. R., and Veasey, L. G.: Management of coarctation of the aorta in infancy, J. Thoracic & Cardiovas. Surg. 37:502, 1959.
18. Clagett, O. T., Kirklin, J. W., and Edwards, J. E.: Variations and pathologic changes in coarctation of the aorta. A study of 124 cases, Surg. Gynec. & Obst. 98:103, 1954.
19. Michaelsson, M.: Personal communication, 1968.
20. Bernhard, W. F., and Norman, J. C.: Cardiac surgery, London, 1967, Butterworth & Co., Ltd., chap. 15, p. 216.
21. Hay, J. D.: Population and clinical studies of congenital heart disease in ... M. J. 2:661, 1...

22. Hoffman J I E. Natural history of congenital heart disease Problems in its assessment with special reference to ventricular septal defects, Circulation 37:97 1968.
23. T wes, R. L Aberdeen, E. Waterston, D J., and Bonham-Carter R E. Coarctation of the orta in infants and children—a review of 333 operat e cases including 179 inf nts, in press.
24. Starker G. W B Surgical experience in the treat ent of congenital mitral stenosis and mitral n ufficiency J Thoracic & Cardiovas. Surg 38 336 1959
25. Creech O Ledbetter M K. and Reemtsma, K Conge tal m tral insufficiency with cleft posterior leaflet Circulation 25:390 1962.
26. Kahn D R Stern A M Sigmann, J M Kirsh M M Lennox, S. and Sloa H: Long-term results of valvuloplasty for mitral insufficiency in children J Thoracic & Cardiovas. Surg 53 1 1967
27. Flege J B Vlad, P and Ehrenhaft, J. L. Congenital mitral incompetence, J Thoracic & Cardiovas. Surg 53:138, 1967
28. Levy M J Varco, R. L., Lillehei, C. W and Edwards, J E. Mitral insufficiency in infants, children, and adolescents, J Thoracic & Cardiovas. Surg 45:434 1963.
29. Tank, E. S. Bernhard, W F and Gross, R. E Surgical anatomy of congenital mitral stenosis, Circulation (Suppl. 2) 36:246, 1967
30. Bloodwell, R. D Hallman, G. L., and Cooley D A.: Cardiac valve replacement in children, Surgery 63 77 1968.

Evaluation of myocardial contractility in man

Hector J. Hermann, M.D.
Rajindar Singh, M.D.
J. Francis Dammann, M.D.
Charlottesville, Va.

With the analysis of the isometric contraction of isolated papillary muscle and intact left ventricle, an assessment of myocardial contractility can be made independent of fiber length or its function as a pump. Experimental studies suggest that the ratios between the first derivative and end-diastolic pressure[1] and integrated isometric tension are constant for a given inotropic state. If so, these ratios should give better indices of contractility than the parameters routinely evaluated in most clinical laboratories.

Furthermore, clinical and experimental observations indicate that the ratio of stroke volume to end-diastolic volume, end-diastolic pressure, estimation of stroke work, and determination of the first and second derivative of the left ventricular pressure are of value used serially in the individual patient, but are of uncertain diagnostic significance in comparing one patient to another.

In the present study, the isovolumetric phase of the left ventricular contraction has been analyzed in 53 patients with several types of heart disease in order to assess the significance and relative value of these experimental findings.

Methods

Fifty-three patients were selected for this study and divided into three different groups. Only those in whom the diagnosis had been established by detailed cardiac catheterization were included.

Group I. The control group of 13 patients consisted of 6 patients without evidence of valvular or myocardial disease who underwent cardiac catheterization because of the presence of functional murmurs and 7 patients with pure mitral stenosis. The existence of mitral insufficiency was ruled out by cineangiography and the patients were considered to have no abnormalities involving the left ventricle.

Group II. This group included 15 patients with unequivocal myocardial disease of different etiology. Eight fulfill the criteria for idiopathic primary myocardiopathy and 7 had evidence of advanced arteriosclerotic heart disease. Except for 3 patients (Nos. 15, 16, and 20), the patients in this group had no evidence of valvular disease.

Group III. This group was comprised of 25 patients with a single valvular lesion causing either severe degrees of mitral or aortic insufficiency or aortic stenosis.

Left ventricular angiograms were ob-

From the Departments of Medicine and Pediatrics, University of Virginia School of Medicine.
Studies supported by National Institutes of Health Research Grant HE [illegible] and T [illegible] C
Received for publication Jan. 2, 1969.
Address correspondence to: Hector J. Hermann, M.D., [illegible] Cardiovascular Laboratory, [illegible] Hospital, 230 East [illegible] St., [illegible]

tained with the injection of 40 to 60 ml of a 75 per cent solution of sodium and methyl glucamine diatrizoate (Renovist Squibb) into the left ventricle (LV) or left atrium (LA) and biplane films (Elema Schonander Stockholm Sweden) or single plane cine exposed at 6 or 30 frames per second respectively Volumes were calculated using the ellipsoid reference figure and the area length method of Dodge and associates[3] and corrected by the regression equation I = I 936 − 3 6 Cineangiograms were obtained with the patients in the RAO position Good correlation between the LV volumes calculated from biplane and single plane frames has been observed in our laboratory[4] as well as by others.[5] The RAO position was selected because it allowed to study the mitral valve and ascertain the existence of mitral insufficiency during the same injection without detriment to the good correlation with biplane LV volumes (r .830 S.E.E 19.8 ml.) It should be noted that in general the largest volumes are slightly overestimated by single plane methods.[4]

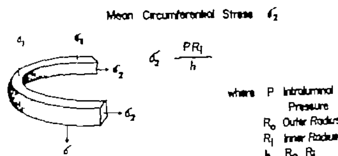


Fig 1 Shows the calculations used in the determination of stress at the equator of the heart and the assumptions they are based on.

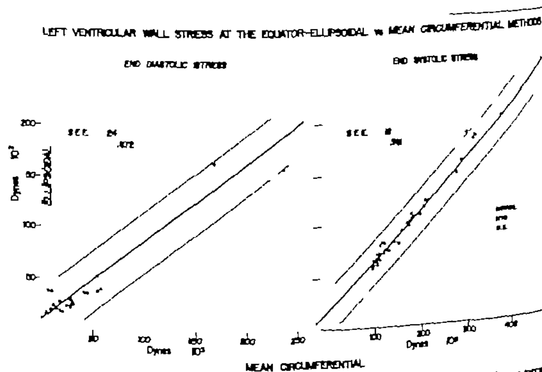


Fig 2 Relationship of left ventricular stress calculated by the simple formula used in the text (mean circumferential) and total ellipsoidal stress. The excellent correlation makes justifiable the use of the simple, less time-consuming formula.

The radii were derived from the formula of the area of an ellipse[4] $RI = \frac{2A}{\pi L}$

Wall thickness (h) was calculated by simple estimation of the width at several points to obtain an average value. This technique of determining LV wall thickness gave almost identical values[4] with the method described by Rackley and associates.

Pressures were obtained immediately before the angiograms by means of No 7 NIH catheters, 100 cm long directly connected to a Statham P23Db transducer which was calibrated before each procedure, balanced before each run and referenced to a zero level 5 cm below the angle of Louis with the patient supine and recorded on an optical recorder at a paper speed of 200 mm. per second. The maximal rate of rise of the left ventricular pressure (dp/dt) was obtained with an R-C differentiating circuit.

Stress (Fig. 1) was calculated at the equator of the left ventricle by the formula $\frac{P \cdot RI}{h}$ where P = LV pressure, RI = inner radius, and h = wall thickness This calculation of circumferential stress or $\sigma 2$ was selected because it is the largest stress at the equator of the ventricle and calculation is simple. There is excellent correlation with the results obtained with more complicated formulas[3] (Fig 2) Stress was expressed in dynes per square centimeter and tension was expressed as *stress* × *wall thickness* ($\sigma 2 \times h$) in dynes per centimeter

Integrated isometric pressure (IIP) was obtained by planimetric integration of the area beneath the isovolumetric phase of the left ventricular pressure tracing (between the end-diastolic point and the opening of the aortic valve) (Fig 3) divided by the isovolumetric contraction time. Integrated isometric stress (IIS) was calculated as $IIS = \frac{IIP \times RI}{h}$ The radius and wall thickness used for these calculations were those calculated from the end-diastolic volumes Although these values change somewhat during the isovolumetric phase of contraction [11] the variations are small and they should not significantly alter the results. Observations in our laboratory using cineangiography have shown that RI and h change less than 4 and 2 mm respectively during this cardiac phase

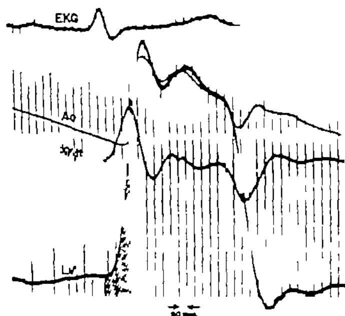


Fig. 1. EKG Electrocardiogram A aortic pressure LV left ventricular pressure dp/dt first derivative of left ventricular pressure IIP integrated isovolumetric pressure (shadowed area).

Table II Statistical analysis of calculated data

Variables	Group I		Group II		Group III	Groups I and III		
dp/dt / IIS								
mean	12 9		4.6		15.3		14 4	
1 S D	3 9	p < 005	1.5	p < 005	5 9		5.2	
S.E M	1		41		1 1		.85	
Ejected fraction								
mean	60		.35		.54		.57	
1 S.D	08	p < .005	15	p < 005	14		12	
S.E.M	03		04		.03		.02	
First derivative (dp/dt)						MI	AI	AS
mean	1486		1000		1764	1602	1891	1811
1 S.D	312	p < 001	260	p < .005	518	424	544	539
S.E M	86		67		103	103	181	204
End-diastolic stress (dynes/cm. 10³)								
mean	20		127		36	42	40	26
1 S D	14	p < .005	69	p < 001	29	33	12	11
S.E.M	2 8		17		5 9	10	10	4
h/RI								
mean	.34		.24		.36	.30	.38	.40
1 S D	07	p < .005	07	p < .005	10	.03	.09	.10
S.E M	02		.01		02	.02	.02	.03
End-diastolic volume (ml /M)								
mean	70		206		146	150	191	87
1 S D	16	p < .005	99	p < 05	76	54	83	7
S E M	4 6		25		15	18	29	3

Abbreviations S D Standard deviation S.E.M., standard error of the mean; MI, mitral insufficiency; AI, aortic insufficiency AS, aortic stenosis.

Results

The values of the measurements and calculations obtained are listed in Table I

The maximal rate of rise of the left ventricular pressure (dp/dt) has been considered a good determinant of ventricular contractility [13,14] It has also been observed to be a function of the heart rate peak ventricular pressure and probably end diastolic volume.[15,4] The analysis of the first derivative from the patients presented herein (Table II) indicates that there is a significant difference between all groups ($p < 001$) The lowest values were found in patients with myocardial disease. However there is a large spread of values in this group as demonstrated by the large standard deviation (S.D 260) The poor clinical diagnostic value of this determination alone is thus clearly evident.

End-diastolic stress (E.D.S.) was significantly higher in the myocardial disease group ($p < 005$) and this was mainly due to the elevated end-diastolic pressures associated with relatively thin left ventricular walls as shown by the significantly smaller h/RI ratio ($p < 005$) Although the wall thickness (h) was somewhat greater in Group III there was no statistically significant difference from those values obtained in patients with primary or arteriosclerotic myocardial disease (Group II)

When the ratio $dp/dt/IIS$ was examined, significantly lower values ($p < .005$) were observed in the myocardial disease group ($4\ 6 \pm 1\ 7$ S.D) Values obtained for Group I were ($12.9 \pm 3\ 9$ S D) and Group III ($15.3 \pm 5\ 9$ S D)

Fig 4 shows the maximal and minimal values of the $\frac{dp/dt}{IIS}$ index calculated for

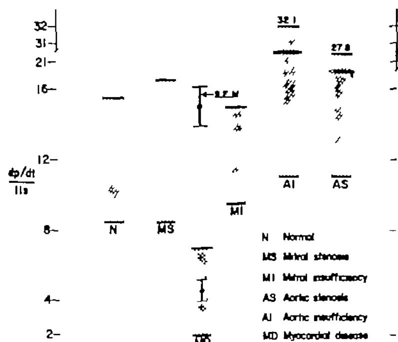


Fig. 4. Histogram showing maximal and minimal values of $\frac{dp/dt}{IIS}$ for each group studied. Significant low values of this ratio for patients with myocardial disease (*MD*) are observed. *S.E.M.* Standard error of the mean.

each type of lesion. There was a clear statistical difference between patients with myocardial disease and the other groups (Table II).

The ejected fraction (E. F.) was significantly lower ($p < .005$) in Group II than in the others (.35 ± .15 and .57 ± .12 respectively). Four patients (Nos. 15, 16, 20, and 28) with a normal E. F. were included in this group since there was clinical and pathologic evidence of myocardial disease. On the other hand, several patients with a low E. F. could not be included in Group II since there was no evidence of myocardial disease, and therefore they had to be included in other groups.

Discussion

End-diastolic stress in myocardial disease. Sandler and Dodge[3] studied tension and stress in the left ventricular muscle in man and have shown that tension and stress increase at a greater rate than the left ventricular pressure, exceeding pressure by as much as 60 to 250 per cent. The greatest stress values were observed in patients with large end-diastolic volumes. They concluded that stress and tension are functions of volume, shape, and wall thickness as well as pressure. In two of their patients with idiopathic myocardial hypertrophy the values of stress found were not significantly different from the end-diastolic stress values obtained in another patient with valvular insufficiency and large left ventricular chambers. In our group of patients with myocardial disease, the end-diastolic stress (initial stress) was significantly higher than in the other groups, including the group of patients with valvular insufficiency and large chamber volumes. Calculations of stress during systole were not determined since they are subject to error which is inherent in the measurement of a contracted irregular ventricular wall.

The observation[3] that wall stress may remain normal in spite of increased wall thickness and elevated tension or pressure was again observed in our study and lends support to the hypothesis that hypertrophy may occur as a consequence of increased pressure or tension in order to keep wall stress within normal limits. This can be observed in our control groups. However

the patients with myocardial disease represent just the opposite situation. Although the diastolic pressures are higher than the other groups, the wall thickness is not significantly greater. Hence the left ventricular end-diastolic wall stress is higher. Our data suggest that in patients with myocardial disease the left ventricular hypertrophy necessary to maintain left ventricular wall stress at a normal level cannot be achieved and the ideal relationship between volume, pressure, and wall thickness cannot be sustained by the diseased ventricular muscle.

Ejected fraction, a controversial index of myocardial disease. Using the area length method of Dodge and associates[2] to calculate the left ventricular volumes, different authors[4, 6] obtained different normal ejected fraction values ranging from .67 to .58 ± .08. These values compare well with those found here. However, when the patients with valvular disease are studied, a larger standard deviation is observed due to the inclusion in this group of patients with low ejected fractions who did not show evidence of myocardial disease by any other standard. They have successfully undergone corrective heart surgery free of cardiovascular complications. As expected, the ejected fraction is low (Table II) in patients with evidence of myocardial disease. However, four patients were included in the group with normal ejected fractions. Two had evidence of severe diffuse coronary artery disease and myocardial fibrosis and one had an old anteroseptal myocardial infarction. Patient 16 with an E.F. of .63 had evidence of acute mitral regurgitation secondary to rupture of papillary muscle. He did not survive surgery, and examination of the heart revealed a large area of fibrosis on the left ventricular wall.

The possibilities of error in estimating these values are several. Sanmarco and associates[7] have observed that the sudden injection into the ventricular chamber of a large volume of contrast material produces an increase of 5 to 15 per cent in end-diastolic volume and 10 to 30 per cent in stroke volume during the filming period. The ejected fraction is consequently overestimated. These changes can be very significant at larger end-diastolic volumes and the ejected fraction is then an exaggeration of the actual value. On the other hand, if

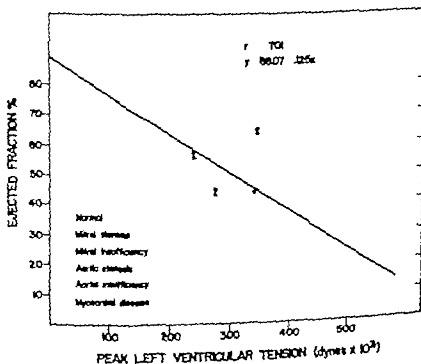


Fig. 5. Ejected fraction plotted as a function of peak systolic tension for Groups I, II, and III. The correlation found for all patients studied is shown.

the volumes are calculated from films obtained at a rather slow speed (4 to 8 per second) the end-systolic point can be missed and the calculation of the E. F is then underestimated. Still another variable is introduced when volumes are determined by single plane films which produce falsely high values in large hearts and low values in smaller ones, thus decreasing and increasing respectively the resultant ejected fraction.

The large standard deviation of the ejected fraction calculated in these patients can be explained by the above errors, and the relative value of this parameter as a basis for the diagnosis and prognosis of patients becomes apparent. Although the ejected fraction has been observed to be related to the stroke volume and to a certain extent to the end-diastolic volumes in normal hearts,[illegible] the data presented herein strongly suggests that this parameter is also an inverse function of the peak left ventricular systolic tension. This is not surprising when one considers the experimental work, using strips of papillary muscle[illegible] and intact hearts[illegible] that has repeatedly shown that during isotonic contraction as the afterload is increased the initial velocity and the extent of fiber shortening are progressively decreased. Fig. 5 shows this relationship (r = −.701) for all patients. Relatively good correlation for clinical purposes was observed in patients with normal left ventricles (r = −.555) and the highest reciprocity (r = −.807) existed in patients with myocardial disease (Fig. 6). On the basis of this observation we can safely assume that any increase in peripheral resistance in patients with myocardial damage should have a deleterious effect on the function of the left ventricle as a pump. On the other hand, patients with aortic stenosis who exhibit a poor ejected fraction should be thoroughly evaluated before being denied the benefits of surgery since the ventricular dysfunction might be at least partially reversible. This has been our experience with four patients of this nature. All of them successfully tolerated open-heart surgery and one showed a normal ejected fraction in a postoperative study when the gradient across the valve was reduced from 90 to 25 mm. Hg across the prosthetic valve.

Clinical significance of $\frac{dp/dt}{I\,I\,S}$ *index.* The

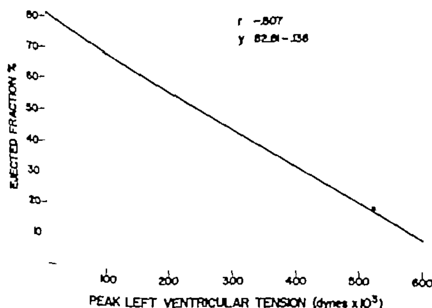


Fig. 6. Relationship of jected fraction and peak systolic tension in patients with myocardial disease (Group II). The best reciprocity between these two parameters is found in this group of patients.

rate of rise of the left ventricular pressure (dp/dt) during isovolumetric contraction is related to the rate of change of wall tension[2] and has been observed to reflect changes in the intensity of the active state.[23,24] Since at any muscle length the rate of tension development is a function of the force velocity relation[25] an estimation of contractility is then possible.

In this study the first derivative of the left ventricular pressure and tension has been found to be poorly correlated to other parameters such as initial fiber length (circumference) end-diastolic and peak systolic pressures and heart rate and the diagnostic significance in many individual cases remains obscure. Although its usefulness to indicate changes in myocardial contractility[2,24,25] is not questioned contradictory values of dp/dt were found in the patients studied here making this determination equivocal from the clinical standpoint.

In the intact hearts of dogs, Reeves and associates[3] found the ratio of dp/dt to end-diastolic pressure to be a good index of contractility defined by the rate of change in force measured by a strain gauge sutured to the left ventricular wall. Siegel and Son-

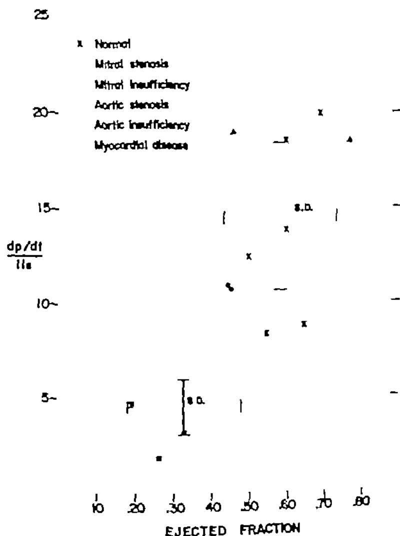


Fig 7 Mean values and standard deviations (*S.D.*) of ejected fraction and $\frac{dp/dt}{I.I.S}$ ratio are shown for patients with myocardial disease and the other groups. The overlap of the standard deviations of the ejected fraction of these two groups of patients is evident. The horizontal dotted line has been drawn at the lowest normal value expected for the $\frac{dp/dt}{I.I.S}$ ratio and clearly separates the patients with myocardial disease.

Sonnenblick,[1] studying isometric contractions of isolated papillary muscles in cats and intact left ventricles in dogs, found that the ratio dp/dt to integrated isometric tension (IIT) was independent of changes in fiber length remains constant for any given state of contractility and varies in a proportional manner to changes in the maximal velocity that shortening the muscle would achieve if carrying no load (V max.) These ratios were analyzed and the relation $\frac{dp/dt}{IIS}$ was observed to correlate well with clinical and pathologic findings in the patients studied thus this ratio constitutes more useful index of myocardial impairment than other parameters measured

Fig. 7 shows a comparison between this ratio and the ejected fraction. All patients with clinical or pathologic indication of myocardial disease showed a low $\frac{dp/dt}{IIS}$ ratio. Using this index, it is possible to differentiate clearly this group with diseased myocardium from the other patients with relatively low ejected fractions and no evidence of irreversible myocardial damage. The fact that patients from Group III tolerated the corrective surgery well suggests that a high value of this index carries a good prognosis. Whether the large variations in ejected fraction observed in this study are due to possible errors in the estimation of this value (vide supra) the depressive action of the pressure volume injecture,[a] or the fact that some patients with valvular abnormalities were in subclinical heart failure at the time of the study is not clear

If the $\frac{dp/dt}{IIS}$ ratio reflects changes in V max., as independent of variation of fiber length alone, and constant for a given contractility it would be possible with this index to define more clearly the inotropic status of the myocardium and its diagnostic value observed herein would then be apparent.

Summary

In 53 patients studied at cardiac catheterization the relationship between the maximal rate of rise of the left ventricular pressure and the integrated isovolumetric stress was observed to be an excellent index of contractility A clearer separation of patients with evidence of myocardial disease was possible with this index than with other parameters assessed

The ejected fraction (fiber-shortening) was noticed to be an inverse function of the peak systolic tension (afterload) as expected from extensive experimental work The highest reciprocity was observed in patients with myocardial disease indicating the probable deleterious effect of an increasing peripheral resistance in this type of patient.

End-diastolic stress was found to be significantly higher in patients with evidence of myocardial damage due to a relatively thinner myocardial wall in this group

REFERENCES

1. Siegel, J H and Sonnenblick, E H Isometric time tension relationships as an index of myocardial contractility Circulation Res. 12:597 1963.
2. Reeves, T J Hefner L L Jones, W B Coghlan C Prieto, G and Carroll, J The hemodynamics determinants of the rate of change in pressure in the left ventricle during isometric contraction, Am. Heart J 60 745 1960.
3. Dodge, H. T Sandler H Ballew D W and Lord, J D The use of biplane angiocardiography for the measurement of left ventricular volume in man Am Heart J 60 762 1960.
4. Hermann, H. J and Bartle S. H. Left ventricular volumes by angiocardiography Comparison of methods and simplification of techniques, Cardiovas. Res 2:404 1968.
5. Greene, D G., Carlisle R. Grant, C., and Bunnell, I L. Estimation of left ventricular volume by one plane cineangiography Circulation 35:61 1967
6. Rackley C. E. Dodge, H T Coble Y D J and H y R. E Method for determining left ventricular mass in man, Circulation 29:666 1964.
7. Noble, F W Electrical methods of blood pressure recording, Springfield, Ill., 1953 Charles C Thomas, Publisher p. 40.
8. Sandler H., and Dodge H. T Left ventricular tension and stress in man, Circulation Res. 13:91 1963
9. Feigl, E. O and Fry D L. Myocardial mural thickness during the cardiac cycle, Circulation Res. 14:541 1964.
10. Fuchmer R. F Initial phase of ventricular systole asynchronous contraction, Am. J Physiol. 184 188, 1956
11. Clagstand, H. E., Taylor R. R., McDonald

R. H Jr and Gilmore, J P Left ventricular circumference changes in right heart by-passed preparations Am J Physiol. 211:681 1966.
12 Mason D T Braunwald E. Ross, J Jr and Morrow A G Diagnostic value of the first and second derivatives of the arterial pressure pulse in aortic valve disease and hypertrophic subaortic stenosis, Circulation 30:90, 1964
13. Gleason W L and Braunwald E Studies on the first derivative of the ventricular pressure pulse in man J Clin Invest 41:80 1962
14 Wallace, A. G Skinner M S Jr and Mitchell, J M Hemodynamic determinants of the maximal rate of rise of left ventricular pressure Am J Physiol 205:30, 1963
15 Bartle S H Sanmarco, M E and Dammann J F J Ejected fraction an index of myocardial function Am. J Cardiol. 15 125 1965.
16 Kennedy J W Baxley W A Figley M D Dodge H T and Blackmon J R Quantitative angiocardiography The normal left ventricle in man Circulation 34:272, 1966.
17 Sanmarco, M E Fronek K. Philips, C. M and Davila, J C. Continuous measurement of left ventricular volume in the dog II Comparison of washout and radiographic techniques with external dimension method Am. J Cardiol 18:584 1966
18. Abbott B C and Mommaerts, W F H M A study of inotrophic mechanism in the papillary preparation J Gen Physiol 42:533, 1959
19 Sonnenblick E H Implications of muscle mechanics in the heart Fed. Proc. 21:975 1962.
20 Sonnenblick, E. H Determinants of active state in heart muscle Force, velocity instantaneous muscle length and time, Fed. Proc. (Suppl.) 24 1396, 1965.
21 Sonnenblick, E. H Force-velocity relations in mammalian heart muscle Am. J Physiol 202:931 1962.
22. Sonnenblick, E. H Braunwald, E., and Morrow A. G. Contractile properties of human heart muscle studies on myocardial mechanics of surgically excised papillary muscles, J Clin. Invest. 44:966 1965
23. Levine H J and Britman, N A. Force velocity relations in the intact dog heart, J Clin Invest. 43 1383 1964
24 Taylor R. R., Ross, J Covell, J W and Sonnenblick, E. H A quantitative analysis of left ventricular myocardial function in the intact sedated dog Circulation Res. 21:99 1967
25 Reeves, T J and Hefner L. L. Isometric contraction and contractility in the intact mammalian ventricle Am. Heart J 64:525, 1962.
26. Sonnenblick, E. H Morrow A. G., and Williams, J F Effects of heart rate on the dynamics of force development in the intact human ventricle, Circulation 33:945 1966
27 Frank, O Zur Dynamik des Herzmuskels, Ztschr Biol. 32:370, 1895.
28. Patterson, S. W Piper H and Starling E. H The regulation of the heart beat, J Physiol. 48:465 1914
29 Wiggers, C. J Some factors controlling the shape of the pressure curve in the right ventricle Am. J Physiol. 33:382, 1914.
30. Rahimtoola S. H. Duffy J P and Swan H J C. Ventricular performance after angiography Circulation 35 70, 1967

An evaluation of antibiotic prophylaxis in cardiac catheterization

Hugh Clark M.D
Rochester N Y

During cardiac catheterization the prolonged presence and manipulation of catheters in the heart may allow repeated introduction of bacteria into the blood stream. As most patients undergoing this procedure have valvular or congenital heart disease, the induced bacteremia may predispose the patients to bacterial endocarditis. Maximal attention to sterile technique and the use of prophylactic antibiotics are measures widely recommended to decrease the risk of endocarditis.[1-3]

The purpose of this report is threefold (1) to determine the incidence of bacteremia in adults undergoing cardiac catheterization (2) to define the bacteria to which the patient is exposed during catheterization and (3) to evaluate the effectiveness of prophylactic antibiotics in preventing bacteremia.

Methods and material

All adult patients admitted to Strong Memorial Hospital for cardiac catheterization over a nine month period (August, 1966 through April 1967) were assigned by a randomization method to one of two protocols for preparation for catheterization. The protocols were identical with the exception that Group A patients received four doses of procaine penicillin 600 000 units intramuscularly every 12 hours, beginning 15 minutes to one hour *before* catheterization. If a patient gave a history of penicillin allergy erythromycin 250 mg by mouth was substituted. This regimen has been standard in the hospital for many years. Patients assigned to Group B received *no* antibiotics before or after catheterization. A mimeographed protocol sheet was placed with each patient's chart on the day prior to catheterization by the cardiology resident but all orders were actually written in the order book by the medical intern. Although the study protocol was explained to the house staff prior to beginning the study 23 patients assigned to the antibiotic group did not receive antibiotics prior to catheterization and this deviation from the protocol may represent a bias on the house staff's part. These patients are henceforth included in Group B and this deviation explains why Group B is larger than Group A. Two patients originally assigned to Group B inadvertently received antibiotics before catheterization and are included in Group A. Thirty two patients received penicillin seven received erythromycin and 83 received no antibiotic.

Blood cultures were taken directly the catheters by the operator who gowned masked and glov

This study was supported in part by Grants HE 7964, HE 5509, and TI-AI-23, United St
Washington, D. C.
Received for publication Oct. 10, 1968.
*Formerly Medical Chief Resident Strong Memorial Hospital, Rochester, N. Y.

mately 5 ml of blood were withdrawn and discarded before drawing the specimen for culture into sterile, individually wrapped disposable syringes. The operator worked in a draped sterile field and did not handle the recording instruments although it is unlikely that the environment approached the relative sterility of an operating room The final culture was frequently taken by a gowned masked and gloved radiologist in a different room and it was considered that in this portion of the procedure contamination was most difficult to control

Four cultures were requested during each catheterization procedure. The first culture was taken from the right heart immediately after recording the pulmonary artery pressure The second culture was taken from the left heart after transseptal passage of the catheter The third culture was taken from an intra arterial needle or cannula after the determination of the cardiac output was completed The final culture was taken from the left heart catheter just before its removal The specimens were immediately injected into flamed citrated bottles and delivered to the microbiology laboratory Aliquots were placed in trypticase soy broth and thioglycolate broth and a pour plate was made. Cultures were incubated at 37° C for 5 days, and if negative the broths were subinoculated into blood agar If no growth was seen on the blood agar in 24 hours the cultures were discarded All isolates were considered as significant Penicillinase was added to all blood specimens taken from patients who received penicillin.

Complications following catheterizations were tabulated and a long term follow-up made whenever possible If a temperature greater than 38° C was recorded in a patient during the 48 hour period following catheterization a thorough examination was performed for signs of infection and blood cultures were again drawn

Results

The 122 patients admitted for cardiac catheterization were included in the study Although the two groups were unequal in size for reasons given above there was no statistically significant difference between the groups with respect to age sex, underlying heart disease and duration of the procedure (Table I)

Positive cultures were obtained in 7 of 39 (18 per cent) of Group A patients and 12 of 83 (14 5 per cent) of Group B patients (Table II) The difference was not statistically significant by chi square analysis. No patient had more than one positive culture. Of 438 cultures taken, 19 (4 3 per cent) were positive, and two cultures contained two organisms. The fourth culture was positive in 10 of 89 specimens (11 2 per cent) taken and when compared with the frequency of positivity in the first three specimens, this was unlikely to have occurred by chance alone (Table III)

Twenty-one organisms were isolated from 19 positive cultures. *Staphylococcus albus* was the most common species found and accounted for 76 per cent of the positive cultures (Table IV) Diphtheroids were present on three occasions. *Sarcina lutea* and an anaerobic spore former were each isolated once. By the disk method 8 of 16 staphylococcal isolates were resistant to penicillin but 13 of 13 tested with methicillin were sensitive. Sensitivities of other organisms to these and to other antibiotics are shown in Table IV

During follow up examination in the hospital 12 of 39 (31 per cent) of Group A patients and 22 of 83 (26 per cent) of Group B patients had a temperature elevation during the 48 hours subsequent to catheterization (Table II) However all cultures taken at the time of temperature elevation were sterile. Fever occurred

Table I *Clinical data*

Variables	Group A	Group B†
Total patients	39	83
male	41%	45%
female	59%	55%
Average age (years)	43 9	47 0
Rheumatic heart disease	69%	74%
Other heart disease	31%	26%
Duration of procedure (hours)	3 3	3 4

*Antibiotic before catheterization.
†No antibiotic before catheterization.

Table II. Results of blood cultures

	Group A*	Group B†
Total patients	39	83
Total blood cultures	140	298
Average no. of cultures per patient	3.6	3.6
Patients with positive cultures	7	12
Per cent of patients with positive cultures	18.0	14.5
Per cent of cultures positive	6.4	4.0
Per cent of patients with fever after catheterization	31.0	26.0

*Antibiotic before catheterization.
†No antibiotic before catheterization.

Table III. Association of fever with positive cultures

Culture	No. of patients/total	%
Fever and positive cultures	6/19	32
Fever and negative cultures	33/103	32
Incidence of positive cultures		
culture no. 1	4/122	3.3
culture no. 2	2/120	1.7
culture no. 3	5/107	4.7
culture no. 4	10/89	11.2 ($p < .025$)

in 6 of 19 (31.6 per cent) of patients who had positive cultures taken at the time of catheterization and in 33 of 103 (32 per cent) of patients who had negative cultures at catheterization (Table III). None of these differences are of statistical significance.

When a chart review was made one month after termination of the study, 48 patients had undergone either cardiac surgery or postmortem examination. Evidence of endocarditis was found in a single patient and is discussed below.

Discussion

Although antibiotic prophylaxis has been widely recommended in preparation for cardiac catheterization, very little information has been available indicating the risk of exposure to bacteremia during the procedure. Kriedberg and Chernoff demonstrated bacteremia in 4.3 per cent of children who received penicillin before catheterization and 4.7 per cent of those who received no antibiotic before catheterization. Although the method of assignment to treatment and control groups was not given, the difference was not significant. Lyon and Gould found bacteremia present during cardiac catheterization in 18 per cent of adult patients given antibiotics and in 17 per cent of those not given antibiotics before the procedure. Neither of these two studies demonstrated a difference in fever following catheterization between the two groups. The increase in frequency of positive

Table IV. Organisms isolated at catheterization and antibiotic sensitivity

Organism	Total	Pen (no./total)	Meth (no./total)	Erythro (no./total)	Chloro (no./total)	Tetra (no./total)	Strep (no./total)	Ceph (no./total)	Amp (no./total)
Staphylococcus albus	16	8/16	13/13	16/16	16/16	12/16	10/13	10/10	5/7
Diphtheroids	1	1/1	1/1	1/1	1/1	1/1	ND*	ND	1/1
Anaerobic spore former	1	0/1	0/1	ND	1/1	1/1	1/1	1/1	1/1
Sarcina lutea	1	ND							
	19								

Abbreviations: Pen, Penicillin; Meth, methicillin; Erythro, erythromycin; Chloro, chloramphenicol; Tetra, tetracycline; Strep, streptomycin; Ceph, cephalothin; Amp, ampicillin.
*ND, Not determined.

cultures in adults may be due to the longer duration of the procedure which often includes both left and right heart catheterization as well as extensive angiocardiographic studies.

The study reported here supports the previously reported work in that it fails to demonstrate protection from transient bacteremia with the use of prophylactic antibiotics. The incidence of positive cultures in adults with and without prophylactic antibiotics agreed closely with the findings reported by Lyon and Gould. As in previous studies, febrile reactions following cardiac catheterization were equally common in treatment and control groups and were not caused by demonstrable infection. Other possible sources of fever include pyrogen on catheters, sensitivity to angiocardiographic materials, and inflammation at the sites of catheter introduction.

Furthermore, the bacteriologic data presented here demonstrate that patients were at greatest risk from the introduction of *Staphylococcus albus*, and that 50 per cent of the strains isolated here were resistant to penicillin. Staphylococci were also the most frequently isolated organisms from blood taken at catheterization in the previous studies. Although no antibiotic sensitivity studies were reported, it is likely that penicillin resistance would have been common. Thus penicillin would not be the drug of choice if it were felt necessary to give an antibiotic prior to catheterization with the goal of preventing subsequent endocarditis. The choice of penicillin by those recommending antibiotic was probably predicated on the assumption that those organisms most commonly causing endocarditis in general would be the organisms to which the patient would receive most exposure during cardiac catheterization, and that is not the case.

The statistically significant increase in frequency of positive cultures taken at the end of catheterization suggests that the duration of the procedure may increase the risk of bacteremia. As noted above, however, it was felt that the final culture was least protected from contamination, and a causal relationship between duration of procedure and increased incidence of positive culture cannot be firmly drawn. That bacteremia is more common in adults than children undergoing catheterization may also be explained by the finding of more frequent positive cultures in more prolonged procedures.

No cases of endocarditis following catheterization were detected in the follow-up examinations of 566 patients studied by the authors of the two earlier studies of antibiotic prophylaxis. In the study reported here, 48 of 122 patients underwent cardiac surgery or postmortem examination subsequent to their cardiac catheterization. Evidence of endocarditis was found in a single patient examined six weeks following cardiac surgery for placement of an aortic graft and prosthetic aortic valve. *Neisseria perflava* was isolated from blood cultures taken during life, and the demonstration of a vegetation on the prosthetic valve ring at autopsy ruled out endocarditis acquired as a result of bacteremia sustained during catheterization.[4]

A review of the literature indicates that endocarditis associated with cardiac catheterization is distinctly unusual if not rare. In several recent reviews of endocarditis in over 500 patients, cardiac catheterization was not mentioned as a predisposing event.[7] Rabinovich[11] has reported a single case and Pankey[12] three cases of endocarditis following catheterization, but inadequate bacteriologic and clinical details were given to evaluate the likelihood of a causative association. As the organisms isolated at catheterization are not common causes of endocarditis, knowledge of the infecting organisms in the cases of Pankey and Rabinovich would be instructive.

The lack of association of endocarditis and cardiac catheterization gains further support from reviews of complications of catheterization performed in over 16,000 patients by three groups of authors.[13-15] Although the duration of follow-up examinations were not given, no cases of endocarditis were detected in the large experience cited.

Summary

The incidence of bacteremia during cardiac catheterization was studied in 122 adult patients and the protective effect of

antibiotic prophylaxis was evaluated in treatment and control groups. Antibiotic prophylaxis did not decrease the incidence of transient bacteremia at cardiac catheterization. Staphylococci were the organisms most frequently isolated from blood cultures taken at catheterization and 50 per cent of the staphylococci were resistant to penicillin. A review of the literature suggests that endocarditis as a sequel to cardiac catheterization is a rare event and may not justify the use of potentially sensitizing agents for prophylaxis.

The author expresses his appreciation to Drs. Paul N. Yu, Bernard E. Schreiner and Gerald W. Murphy for allowing this study to be done on patients referred to them for cardiac catheterization, and to Mrs. Helen Short of the bacteriology laboratory for technical assistance.

REFERENCES

1. Zimmerman, H. A. Intravascular catheterization, Springfield, Ill., 1959, Charles C Thomas, Publisher, chap. 1, p. 5.
2. Wood, P.: Diseases of the heart and circulation, ed. 2, Philadelphia, 1957, J. B. Lippincott Co., p. 180.
3. Friedberg, C. K.: Diseases of the heart, ed. 3, Cambridge, 1966, Harvard University Press, p. 198.
4. Kriedberg, M. E., and Chernoff, H. L. Ineffectiveness of penicillin prophylaxis in cardiac catheterization, J. Pediatrics 66:286, 1965.
5. Goold, L., and Lyon, A. F. Penicillin prophylaxis cardiac catheterization, J. A. M. A. 202:210, 1967.
6. Clark, H. and Patton, R. D. Postcardiotomy endocarditis due to Neisseria perflava on a prosthetic aortic valve, Ann. Int. Med. 68:386, 1968.
7. Friedberg, C. K., Goldman, H. M., and Field, L. E. Study of bacterial endocarditis. Comparisons in ninety five cases, Arch. Int. Med. 107:6, 1961.
8. Geraci, J. E. Antibiotic therapy of bacterial endocarditis. Therapeutic data on 172 patients seen from 1951 to 1958. Additional observations on short-term therapy (two weeks) for penicillin sensitive organisms, M. Clin. North America 42:1101, 1958.
9. Vogler, W. R., et al. Bacterial endocarditis: Review of 148 cases, Am. J. Med. 32:910, 1960.
10. Lerner, P. I., and Weinstein, L. Infective endocarditis in the antibiotic era, New England J. Med. 274:199, 259, 323, 388, 1966.
11. Rabinovich, S., Evans, J., Smith, I. M., et al. A long-term view of bacterial endocarditis. 337 cases 1924-1963, Ann. Int. Med. 63:185, 1965.
12. Pankey, G. A. Subacute bacterial endocarditis at the University of Minnesota hospitals, 1939-1959, Ann. Int. Med. 55:550, 1961.
13. Cournand, A., et al. Report of committee on cardiac catheterization and angiocardiography of the American Heart Association, Circulation 7:769, 1953.
14. Bagger, M., Biorck, G., Björk, V. O., et al. On methods and complications in catheterization of heart and large vessels, with and without contrast injection, Am. Heart J. 54:766, 1957.
15. Wennevold, A., Christiansen, I., and Lindeneg, O. Complications in 4,413 catheterizations of the right side of the heart, Am. Heart J. 69:173, 1965.

Experimental and laboratory reports

Effects of isoproterenol on hemodynamic alterations, myocardial metabolism, and coronary flow in experimental acute myocardial infarction with shock

Leslie A. Kuhn, M.D.
Howard J. Kline, M.D.
*Philip Goodman, M.D.**
*Charles D. Johnson, M.D.**
Anthony J. Marano, M.D.
New York, N. Y.

Because of the continuing high mortality rate associated with shock following acute myocardial infarction, attention has been directed to the treatment of this syndrome with drugs other than those traditionally employed, metaraminol or norepinephrine. It has been argued that these agents, which have both inotropic and peripheral vasopressor effects, produce an undesirable increase of the pressure against which the left ventricle must work and are therefore deleterious to the function of the acutely ischemic myocardium. Isoproterenol, which also possesses inotropic effects, does not directly increase arterial pressure. Therefore, its use has been advocated in various forms of shock as well as in that following acute myocardial infarction, and apparent beneficial effects have been reported in a variety of conditions characterized by low cardiac output.[1,2] However, hemodynamic data concerning the use of isoproterenol in acute myocardial infarction with shock are sparse, and its precise value and hazards in this syndrome have not been defined clearly. Despite its apparent usefulness in other forms of shock, certain of its effects would appear to be of more critical importance in acute myocardial infarction. These include chronotropic effects on the ischemic left ventricle, the increase of left ventricular oxygen requirement, and in many instances the failure to maintain adequate coronary perfusion pressure. It was our purpose to investigate the effects of this drug on hemodynamic and cardiac metabolic alterations in this syndrome.

Methods

We studied 19 dogs anesthetized with a solution of 0.4 per cent chloralose and 4 per cent urethane given intravenously in doses sufficient to produce light anesthesia. The total dose administered ranged from 1.2 to 1.4 Gm. of chloralose and 12 to 14 Gm. of urethane.

A thoracotomy was performed in the fourth right interspace and artificial ventilation with air was maintained through an endotracheal tube. Fig. 1 is a schematic representation of the experimental ar-

From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, New York, N. Y.
Supported by Research Grant HE-04132 from the National Institutes of Health, United States Public Health Service.
Received for publication Aug. 14, 1968.
*Trainee of United States Public Health Service Training Grant No. 5 T1 HE-5[illegible]

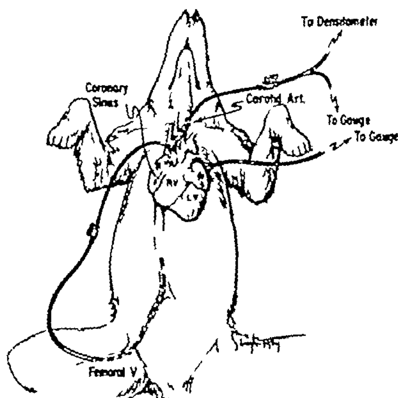


Fig 1 Experimental arrangement. See text for details.

rangement. After a small incision was made in the pericardium a large polyethylene catheter with a flanged end was inserted via the right atrial appendage approximately 2 cm. into the mouth of the coronary sinus and sutured in place. This catheter was connected by a small length of Tygon tubing to a large-bore Bardic catheter which was inserted into a femoral vein. A three-way stopcock was placed in the coronary sinus-femoral vein circuit for periodic sampling of coronary sinus blood and for measurement of coronary sinus flow by gravity drainage. Preliminary experiments with this tubing arrangement indicated that the coronary sinus flow measured by gravity drainage at the far end of the Bardic catheter was the same as that measured by gravity drainage from the short polyethylene catheter introduced into the coronary sinus. In addition in a few experiments, coronary sinus flow was measured by an electromagnetic flowmeter applied to the tubing system this flow was the same as that obtained from the end of the short catheter introduced directly into the coronary sinus. Therefore although the resistance to coronary sinus outflow imposed by the shunt from the coronary sinus to the femoral vein was not determined directly the shunt did not elevate resistance to coronary sinus outflow sufficiently to affect coronary sinus flow

Through the same chest incision polyethylene tubing was inserted through a segmental pulmonary vein into the left atrium for measurement of left atrial pressure The zero reference level was the mid left atrium as determined by direct inspection A thin walled Lehman aortographic catheter was passed in a retrograde direction from a femoral or carotid artery into the ascending aorta just distal to the coronary arterial orifices The catheter was first inserted into the left ventricle and then withdrawn until an aortic pressure pulse appeared on the monitoring screen it was used for injection of plastic microspheres, measurement of central aortic pressure, withdrawal of arterial blood for sampling and cardiac output determination

Myocardial infarction with

produced by our modification[3] of the technique of Agress and co-workers.[4] Polystyrene microspheres, 3 to 4 mg. per kilogram and 325 micra in diameter suspended in 15 per cent acacia in normal saline were injected with a pressure injector into the ascending aorta during transient asystole produced by a rapid intravenous injection of 0.4 mg. per kilogram of acetylcholine.

At least a 30 per cent fall in cardiac output and mean central aortic pressure, persisting for 30 minutes following coronary embolization was required for the animal to be considered in shock and for further studies to be performed. About 75 per cent of all animals developed shock with only one injection of the microspheres several required two or three injections of microspheres before the desired hemodynamic alterations could be produced. Some did not develop shock even after multiple injections of microspheres and these animals were not studied further.

This method consistently produces diffuse subendocardial infarction involving both ventricles in those that survive six or more hours after coronary embolization. The animals in this study were put to death after the experiment, before sufficient time had elapsed to develop these pathologic changes.

Isoproterenol was infused intravenously by a constant infusion pump as a solution in 5 per cent glucose in water in a dose of 2 to 6.6 μg per minute for a period of one hour beginning 30 minutes after coronary embolization by this time, a stable hemodynamic state had been obtained. Since the results in animals studied at these various dose levels were not significantly different they will be discussed subsequently as a homogeneous group.

Cardiac output coronary sinus flow and central aortic and left atrial pressures were determined first after anesthesia then 30 minutes following coronary embolization when there was a stable hemodynamic state after 15 minutes and after 60 minutes of isoproterenol infusion and 15 minutes after discontinuation of isoproterenol. Samples were drawn simultaneously from the aorta and coronary sinus at these intervals for determination of pH pO_2 and the concentration of hemoglobin lactate and pyruvate. Similar determinations and sampling were performed at similar intervals in animals receiving no therapy following coronary embolization.

Pressures were determined with Statham strain gauges and were recorded on a multichannel oscilloscopic recorder. Cardiac output was measured by the dye dilution technique indocyanine green dye was injected into a central vein or the right atrium and blood samples were drawn from the ascending aorta through a densitometer by a constant-speed motor-driven syringe. The resultant curve was replotted on semilog paper. Circulation time from the right atrium to the aorta was measured from the onset of injection of the dye to the initial recorder deflection indicating the appearance of dye at the ascending aorta. pO_2 and pH were determined by Instrumentation Laboratory electrodes, and hemoglobin was determined by a Coleman Universal spectrophotometer. Lactate and pyruvate were measured by the enzymatic method of Horn and Bruns[6] "excess lactate" of the left ventricle was calculated by the method of Huckabee.[7] It was assumed that the left ventricle produced the excess lactate determined by Huckabee's formula $XL = (L_v - L_a) - (P - P_a) \times (L_a/P)$ where XL stands for excess lactate v coronary sinus a aorta L mM of lactate and P mM of pyruvate.

Systemic vascular resistance left ventricular work, left ventricular oxygen consumption coronary vascular resistance, and mechanical efficiency of the left ventricle were calculated from the above measurements, using conventional formulas. Left ventricular weight was calculated according to the method of Herrmann.[8] We assumed that the coronary sinus drainage represented almost entirely left coronary arterial blood.[9] In the coronary arterial patterns of the dog (left coronary artery predominant[9,10]) the left coronary artery supplies the whole left ventricle but may also supply a portion of the right ventricle.

Oxygen consumption of the left ventricle was calculated as the product of coronary flow in milliliters per 100 Gm. of the left ventricle per minute and the left ventricular arteriovenous oxygen differ

ence (milliliters of oxygen per 100 milliliters of blood) Oxygen saturation of blood from the coronary sinus and aorta was calculated from the measured oxygen tension (after correcting for the temperature and pH of each sample) and the oxygen dissociation curve of hemoglobin. Oxygen capacity was calculated from the measured hemoglobin concentration assuming that each gram of hemoglobin when fully saturated, carried 1.34 ml. of oxygen. By knowing the percentage of oxygen saturation and oxygen capacity the oxygen content of the specimen could then be determined. Because a small portion of the coronary sinus drainage may derive from the right ventricle and because most but not all, left coronary arterial blood drains into the coronary sinus,[9] the method of calculation of left ventricular oxygen consumption must be considered an approximation of actual left ventricular oxygen consumption, though it most probably reflects directional changes accurately

Left ventricular mechanical efficiency was determined by dividing the work of the left ventricle (in kilogram meters per minute) by the energy cost of the left ventricular work. The latter was calculated as left ventricular oxygen consumption (milliliters per minute) × 2 06 this is the energy equivalent in kilogram meters of 1 ml. of oxygen consumption Left ventricular work was calculated as the product of mean arterial pressure and cardiac output.

Results

Hemodynamic and electrocardiographic alterations The results in the isoproterenol treated and nontreated animals are indicated in Table I and expressed graphically in Fig 2

Thirty minutes following coronary embolization prior to isoproterenol infusion there were significant declines ($p < 0.01$) of cardiac output stroke volume and aortic pressure Systemic vascular re

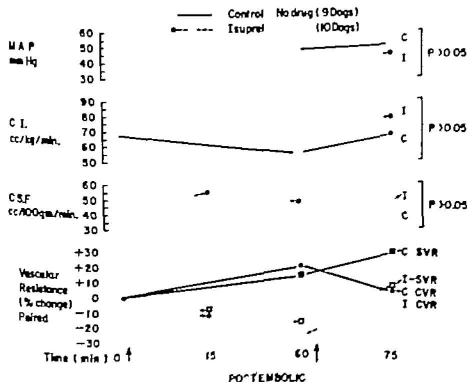


Fig 2. Comparison of hemodynamic [illegible] in the [illegible] period in animals receiving isoproterenol and those receiving no therapy following coronary embolization. Isoproterenol was administered during the period demarcated by the arrows. M A P, mean aortic pressure; C.I, cardiac index; C S F, coronary sinus flow; SVR, systemic vascular resistance; CVR, coronary vascular resistance.

Table I. Hemodynamic alterations in dogs receiving isoproterenol (I) and in those receiving no therapy (C) following coronary embolization

Hemodynamic factors		No. of dogs	Pre-embolic	Postembolic: Before therapy	Postembolic: During isoproterenol (or no therapy in controls) (15 min.)	Postembolic: During isoproterenol (or no therapy in controls) (60 min.)	Postembolic: No drug (75 min.)
Cardiac output (mL/kg/min.)	I	10	128 (16)	79 (9)	88 (9)	78 (10)	78 (6)
	C	9	147 (4)	68 (10)		56 (9)	67 (15)
Central aortic pressure (mm. Hg)							
Systolic	I	10	92 (6)	72 (6)	84 (8)	74 (8)	77 (10)
	C	9	106 (8)	70 (7)		64 (9)	74 (10)
Diastolic	I	10	56 (5)	36 (5)	35 (4)	31 (5)	35 (7)
	C	9	68 (6)	43 (6)		39 (7)	42 (7)
Mean	I	10	70 (6)	46 (11)	48 (5)	40 (4)	46 (7)
	C	9	84 (6)	51 (7)		49 (7)	51 (8)
Heart rate (beat per minute)	I	10	144 (14)	133 (10)	150 (14)	136 (8)	116 (14)
	C	9	152 (23)	143 (15)		140 (13)	129 (11)
Stroke volume (mL)	I	10	26 (4)	17 (2)	18 (3)	16 (3)	19 (2)
	C	9	21 2 (3 0)	10 3 (1 1)		10 3 (2 6)	12 3 (3 1)
Left atrial mean pressure (mm. Hg)	I	10	3 (1)	3 (1)	2 (1)	1 (1)	1 (1)
	C	9	1 (1)	1 (1)		1 (1)	1 (1)
Circulation time (right atrium-aorta) (sec.)	I	10	14 (0 4)	15 (0 5)	14 (0 4)	15 (0 5)	13 (0 7)
	C	9	12 (0 3)	15 (0 3)		15 (0 7)	14 (0 4)
Systemic vascular resistance (dynes/sec./cm.⁻⁵)	I	10	1 586 (197)	1 28 (188)	1 578 (285)	1 424 (132)	1 812 (129)
	C	9	1 944 (181)	2 4 0 (253)		2 813 (290)	3 259 (771)
Coronary sinus flow (ml./100 Gm. LV/min.)	I	10	60 (7)	43 (4)	52 (8)	47 (5)	47 (10)
	C	9	56 (9)	43 (4)		38 (5)	42 (5)
Coronary vascular resistance (dynes/sec./cm.⁻⁵)	I	10	81 400 (10 250)	76 576 (10 250)	66 326 (7 838)	56 678 (10 250)	77 782 (24 118)
	C	9	99 488 (17 486)	74 164 (9 044)		89 841 (18 088)	76 576 (14 471)

Mean values with standard error in parentheses. Average weight (Kg.): Isoproterenol-treated = 27; controls = 24.5.
*Statistically significant difference (p < .05) (from the first postembolic determination) between animals receiving isoproterenol and those receiving no therapy.

sistance increased slightly and heart rate declined slightly ($p < 0.05$). Coronary sinus flow and coronary vascular resistance diminished ($p < 0.05$); the decline of coronary vascular resistance probably attributable to the effects of acute myocardial ischemia. To explain this, it is postulated that some degree of coronary vasodilatation may occur in response to acute myocardial ischemia even though many vessels of the caliber of the microspheres are presumably obstructed as a result of microsphere injection.

After 15 minutes of isoproterenol infusion, systemic and coronary vascular resistance declined ($p < 0.05$); cardiac output, heart rate, stroke volume, coronary sinus flow, and aortic pressure increased slightly but without significance statistically ($p > 0.05$). Continued infusion of isoproterenol for one hour resulted in a decline of aortic pressure, coronary sinus flow, cardiac output, and stroke volume to levels obtained prior to the initiation of the isoproterenol infusion. Systemic and coronary vascular resistances diminished progressively. Left atrial pressure did not change appreciably with isoproterenol. After discontinuation of the isoproterenol, heart rate diminished and there was a rise of systemic and coronary vascular resistances to levels obtained prior to infusion.

Comparison of the results in animals given isoproterenol with those of animals receiving no therapy following coronary embolization indicates little apparent difference between the groups, except in the response of systemic and coronary vascular resistances. Systemic vascular resistance showed significant declines with isoproterenol and moderate increases when no therapy was administered. Coronary vascular resistance also declined progressively with isoproterenol. Control animals receiving no therapy following coronary embolization had somewhat higher initial systemic and coronary vascular resistances than did animals receiving isoproterenol in the postembolic period. Nevertheless, the subsequent alterations of vascular resistances in these groups were in different directions as indicated in Table I. Although cardiac output and coronary sinus flow increased in some animals initially with isoproterenol administration ($p > 0.05$), this increment was not maintained and there was no significant difference between the two groups 90 minutes after embolization following one hour of isoproterenol administration.

An attempt was made to determine whether the level of postembolic systemic vascular resistance prior to therapy was important in determining the hemodynamic response to subsequent isoproterenol administration. Five animals had pretreatment systemic vascular resistance levels lower than 1,600 dynes/sec./cm.$^{-5}$ (average 1,534) and 5 showed more elevated levels of pretreatment systemic vascular resistance (average 2,164 dynes/sec./cm.$^{-5}$). No significant differences were observed between the two groups in hemodynamic or cardiac metabolic responses to isoproterenol.

There was an increased incidence of ventricular fibrillation occurring at least 30 minutes after embolization in dogs given isoproterenol (4 of 13) compared to those receiving no therapy (1 of 11), but the numbers of dogs in each group were too few to form definite conclusions about the significance and consistency of these observations.

Metabolic alterations. Alterations of left ventricular oxygen consumption, mechanical efficiency, and lactate extraction or production are indicated in Table II. Comparison of isoproterenol treated and nontreated animals is shown graphically in Fig. 3.

Following coronary embolization prior to isoproterenol infusion, there was a decline of left ventricular oxygen consumption, mechanical efficiency, and arterial pH ($p < 0.05$). Isoproterenol produced a moderate increase in left ventricular oxygen consumption ($p > 0.05 < 0.10$), whereas this declined progressively in dogs receiving no therapy. Mechanical efficiency of the left ventricle was unchanged during isoproterenol therapy but rose when it was discontinued. There was no difference in mechanical efficiency between the two groups. Progressive acidosis was observed in both control and treatment groups.

Left ventricular "excess lactate" production diminished moderately after

Table II Cardiac metabolic alterations in dogs receiving isoproterenol (I) and in those receiving no therapy (C) following coronary embolization

Metabolic factors		No. of dogs	Pre-embolic		Postembolic: Before therapy		Postembolic: During isoproterenol (or no therapy in controls) (15 min.)		Postembolic: During isoproterenol (or no therapy in controls) (60 min.)		Postembolic: No drug (75 min.)	
Arterial-coronary sinus O_2 difference (ml. O_2/100 ml. blood)	I	10	10 9	(0 2)	9 8	(0 6)	8 7	(0 4)	7 6	(0 6)	6 9	(0 5)
	C	9	9 2	(0 7)	7 6	(0 5)			7 4	(0 6)	6 8	(0 6)
Left ventricular (LV) O_2 consumption (ml. O_2/100 Gm. LV/min.)	I	10	6 53	(0 81)	4 18	(0 61)	4 55	(1 09)	4 05	(0 35)	3 25	(0 68)
	C	9	5 36	(0 68)	3 21	(0 39)			2 83	(0 37)	2 65	(0 21)
LV mechanical efficiency (%)	I	10	23 0	(3 3)	17 1	(7 1)	19 8	(6 8)	18 5	(8 9)	26 3	(6 9)
	C	9	27 8	(7 0)	18 2	(4 4)			19 9	(6 3)	21 3	(6 3)
Arterial blood lactate (mM./L.)	I	10	718	(037)	753	(041)	784	(061)	1 00	(068)	815	(054)
	C	9	472	(035)	629	(043)			644	(099)	712	(065)
Coronary sinus blood lactate (mM./L.)	I	10	563	(023)	783	(050)	743	(056)	930	(066)	797	(046)
	C	9	335	(034)	592	(058)			539	(052)	539	(035)
Arterial blood pyruvate (mM./L.)	I	10	049		053		050		051		053	
	C	9	042	(002)	046	(003)			043	(003)	044	(003)
Coronary sinus blood pyruvate (mM./L.)	I	10	031		039		042		042		034	
	C	9	025	(002)	033	(003)			036	(003)	036	(004)
LV "excess lactate" (mM.)	I	10	0 00		+1 372	(0 38)	+1 376	(0 39)	+1 588	(0 37)	+1 027	(0 49)
	C	9	0 00		+1 314	(0 501)			+ 044	(035)	+ 466	(0 203)
Lactate extraction ratio (%)	I	10	22	(1 6)	11	(0 1)	5	(0 77)	7	(0 52)	5	(0 72)
	C	9	29	(0 4)	12	(0 2)			20	(0 4)	18	(0 3)
Arterial pH	I	10	7 42	(02)	7 33	(03)	7 30	(03)	7 23	(05)	7 26	(01)
	C	9	7 39		7 28				7 26		7 24	
Coronary sinus pH	I	10	7 39	(02)	7 30	(03)	7 28	(04)	7 20	(06)	7 24	(01)
	C	9	7 36		7 23				7 22		7 20	

Mean values with standard error in parentheses.
Statistically significant difference (p < 0.05) in change from the first postembolic determination between animals receiving isoproterenol and those receiving no therapy.

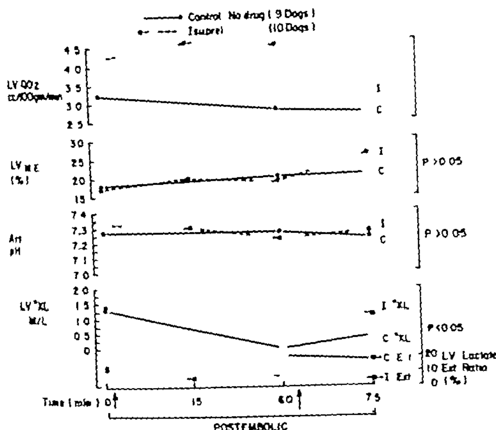


Fig. 3 Comparison of metabolic alterations occurring in the postembolic period in animals receiving isoproterenol and those receiving no therapy following coronary embolization Isoproterenol was administered during the period demarcated by the arrow. *LVO₂*, Left ventricular oxygen consumption *LV M.E.*, left ventricular mechanical efficiency *LV XL*, left ventricular excess lactate production

early postembolic period when no treatment was given ($p < 0.05$) but increased progressively during isoproterenol infusion ($p < 0.05$) diminishing after discontinuation of the isoproterenol. Differences between the groups in regard to excess lactate production were significant statistically ($p < 0.05$) Table III indicates that isoproterenol administration was not associated with diminution or disappearance of postembolic left ventricular excess lactate production in any of the 7 animals in which anaerobic myocardial metabolism was evident prior to therapy

Discussion

Isoproterenol has been used with increasing frequency in the treatment of shock following acute myocardial infarction its use has been based on the belief that this drug provides the advantages of a purely inotropic agent without the concomitant disadvantage of increasing the pressure against which the left ventricle must contract by peripheral arteriolar constriction

Our results indicate that isoproterenol produced a slight transitory increment of cardiac output and coronary flow in some animals with experimental acute myocardial infarction with shock but increases were not significant at the 5 per cent level for the group as a whole Anaerobic metabolism in the acutely infarcted left ventricle was not favorably affected and left ventricular lactate production increased progressively during isoproterenol administration This suggests that the favorable effects attributed to isoproterenol in the treatment of other forms of shock [2] cannot necessarily be transferred to the hemodynamic and metabolic alterations occurring in acute myocardial infarction with shock In the dosage range studied in our experiments (2 to 6 6 μg per minute) no differ

Table III. Left ventricular excess lactate production in dogs receiving isoproterenol and in those receiving no treatment following coronary embolization

	N of dogs	N with postembolic LV excess lactate	N with diminution or disappearance of LV excess lactate
Isoproterenol	10	7	0
No therapy	9	8	1

ence in response to isoproterenol at the various dosage levels was noted. These dosages embraced those employed in almost all reported clinical and experimental studies with this drug, but were slightly exceeded in some instances in one report[11] and were considerably exceeded in another.[9] Of course, it is conceivable that higher or lower dosage levels might have produced different effects, but we can present none of our own data to support this view.

Analysis of studies of isoproterenol in clinical or experimental acute myocardial infarction with shock indicates variability of reported results. Detailed hemodynamic measurements have been obtained in 31 patients analyzed by four different investigators.[13,1,14] Variable though often transitory or no rises of cardiac output were obtained. No apparent definitely favorable effect on the mortality rate was established. The one patient reported by McLean and associates[1] demonstrated a rise of cardiac output with no appreciable rise of arterial pressure, but in this patient the shock-like state following acute myocardial infarction may have been related to complicating ventricular tachycardia, relief of which could have been a factor in the subsequent rise of cardiac output. Significant rises of arterial pressure and average cardiac output were reported in eight patients by Morse and associates, but full details of the protocols are not available. Pretreatment bradycardia and the use of plasma volume expansion were additional factors in this study which complicate interpretation of the precise effects of isoproterenol. In Smith and co-workers'[12] series of 11 patients treated with isoproterenol, rise of cardiac index was reported in 8 patients, but the duration of infusion was from 10 to 45 minutes. Our results indicate that transient rises of cardiac output were obtained when isoproterenol was infused, but when the observations were extended for 1 hour of therapy, there was return to pretreatment levels. The report of Gunnar and associates[13] of 11 patients stressed the transient nature of improvement of cardiac output, the lack of adequate arterial pressure rise with isoproterenol, and the frequent clinical deterioration accompanying the use of this drug in acute myocardial infarction with shock.

In experimental acute myocardial infarction, Cronin's[14] studies demonstrated some hemodynamic improvement with the use of isoproterenol, but these animals had relatively little hypotension (mean arterial pressure, 89 mm. Hg) prior to drug infusion and studies were performed after only 15 minutes of drug administration. Although more sustained improvement of cardiac output following the use of isoproterenol in experimental acute myocardial infarction was reported by Dietzman and associates,[17] administration of the drug was initiated 5 minutes following coronary embolization. In our experience with plastic sphere coronary embolization a steady hemodynamic state does not generally occur in so short an interval following embolization; further alterations of arterial pressure and cardiac output often being noted after this interval when no treatment is administered. Therefore, the efficacy of a therapeutic agent administered so soon after embolization may be difficult to assess. Fearon's[13] recently reported study in which variable but high doses of isoproterenol were employed, doses several times greater than those employed clinically, indicated increase of cardiac output and aortic pressure attributable to this drug. However, there was no consistent improvement of left ventricular lactate extraction or production and there was a high incidence of ventricular fibrillation with the dosage range studied (75 per

ent). The use of propranolol immediately prior to isoproterenol infusion, the simultaneous use of lidocaine, and the varying dosage within each experiment (to keep heart rate below a specified level) confuse interpretation of the results.

Not only the duration of drug administration, but also the pretreatment state of myocardial functional derangement would appear to be of importance in determining the efficacy of isoproterenol and may account for apparent differences in reported results. In this regard Hood and associates have demonstrated enhanced left ventricular function with isoproterenol administration in dogs with anatomically small acute myocardial infarction (but not shock) but there was a considerably attenuated response in those animals in which more than 20 per cent of the left ventricle was infarcted. Similarly the inotropic response to isoproterenol of the experimentally pressure loaded left ventricle may be considerably diminished in acute myocardial infarction.[18] In congenital heart disease also dissimilar effects of isoproterenol on ventricular function have been described depending on the severity of pretreatment myocardial dysfunction. Increased heart size and diminished efficacy of ventricular emptying, as manifested by an increase in end-diastolic volume and decrease of ejection fraction, were noted when isoproterenol was administered to patients with initially severe myocardial impairment.[20]

In shock associated with acute myocardial infarction, the failure of isoproterenol to produce sustained hemodynamic improvement and to reverse left ventricular anaerobic metabolism may be closely related to its failure to raise aortic pressure sufficiently to maintain adequate coronary flow and myocardial perfusion. Despite reduction or lack of increase of the pressure against which the left ventricle worked, the metabolic state of the ischemic left ventricle was not improved by this inotropic agent. This is in distinct contrast to the results obtained when coronary perfusion pressure is increased mechanically in acute myocardial infarction with shock, even though no inotropic agent is administered, or when an agent with both inotropic and peripheral arteriolar constrictive effects is utilized. Under these circumstances coronary flow increases considerably, cardiac output is increased, and anaerobic metabolism of the acutely ischemic left ventricle is in most instances reversed. These beneficial effects may be noted when aortic pressure is raised from shock levels despite the concomitant increase of the afterload of the ventricle. Daniell and associates have demonstrated in the normal isoproterenol-treated dog sharp diminution of coronary flow and myocardial contractile force as well as evidence of anaerobic ventricular metabolism concomitant with a decreased coronary perfusion pressure. The effects were intensified by sustained infusion of isoproterenol. Moreover, the depressed myocardial function and ventricular anaerobic metabolism were counteracted by mechanical maintenance of high aortic pressure. In these investigations, the apparent mechanism by which coronary flow limited ventricular contractility in the isoproterenol-stimulated heart was that of transient hypoxia.

We do not have sufficient data to determine whether an increase in the dose of isoproterenol would have produced different effects. As indicated previously, the dosage employed in our experiments was comparable to or exceeded that used in reported clinical or experimental investigations with the exception of Fearon's studies. The results of those studies suggest that hemodynamic improvement may be expected at considerably higher dose levels but the incidence of associated ventricular fibrillation was quite high, perhaps limiting the clinical feasibility of very high doses of isoproterenol in acute myocardial infarction.

Although blood volume measurements were not performed in our experiments, previous experience indicates that only a moderate and variable decline of blood volume occurs in the first few hours following coronary embolization (10 to 15 per cent). It is probable therefore that a lack of a sustained hemodynamic response to isoproterenol cannot be attributed to a critical reduction of blood volume, although it would be of interest to determine the response to this agent when the blood volume was increased following acute myocardial infarction. Further increment of

cardiac output with the addition of dextran in isoproterenol treated animals with myocardial infarction and shock has been reported[1] but there were no accompanying measurements of blood volume in these studies.

In our experiments, little diminution of coronary sinus oxygen or widening of arterial-coronary sinus oxygen difference was noted during isoproterenol administration despite the development of anaerobic left ventricular metabolism as determined from "excess lactate" production. This is in keeping with similar findings of *Daniell and associates*[30] *as well as those of* Doersching and Glaviano[3] in hemorrhagic shock. A possible explanation for these observations may be derived from the experiments of Greene and associates,[33] which suggested shunting of coronary flow away from intramyocardial nutrient vessels during intravenous administration of isoproterenol.

The results of our experiments as well as analysis of other reports suggest that considerable caution be used in the administration of isoproterenol in acute myocardial infarction with shock and that attainment of adequate levels of coronary perfusion pressure is most probably an important factor in the successful treatment of this syndrome.

Summary

Hemodynamic and cardiac metabolic effects were investigated in dogs given isoproterenol (2 to 6.6 μg per minute) and in those receiving no therapy following production of acute myocardial infarction with shock by plastic sphere coronary embolization.

Following coronary embolization before therapy there were significant declines in cardiac output, aortic pressure, coronary sinus flow, and left ventricular mechanical efficiency. Left ventricular "excess lactate" was produced in almost all animals. After 15 minutes of isoproterenol infusion there were slight increases of cardiac output, heart rate, left ventricular work, coronary flow, and left ventricular oxygen consumption. Left atrial and aortic pressures, left ventricular mechanical efficiency, and "excess lactate" production were unchanged. Systemic and coronary vascular resistances declined moderately. With continued infusion for one hour, cardiac output, aortic pressure, and coronary sinus flow declined to levels obtained prior to infusion and left ventricular "excess lactate" production increased further. There was progressive decline of arterial pH. In comparison to those receiving no therapy, isoproterenol treated animals had significantly lower systemic and coronary vascular resistances and greater left ventricular "excess lactate" production.

It is concluded that isoproterenol produces moderate initial hemodynamic improvement in acute myocardial infarction with shock, but this is not sustained and left ventricular "excess lactate" production is unfavorably affected. It is suggested that lack of significant sustained hemodynamic improvement and continued anaerobic metabolism with isoproterenol therapy in acute myocardial infarction with shock most probably results from failure to raise the critically low coronary perfusion pressure sufficiently to produce adequate oxygenation of the acutely ischemic left ventricle.

The technical aid of Mr. John L. King, Jr., and Miss Allison Meader is gratefully acknowledged.

REFERENCES

1. McLean, L. D., Duff, J. H., Scott, H. M., and Peretz, D. I.: Treatment of shock in man based on hemodynamic diagnosis, Surg. Gynec. & Obst. 120:1, 1965.
2. Elliott, W. C., and Gorlin, R.: Isoproterenol in treatment of heart disease, J. A. M. A. 197:93, 1966.
3. Kuhn, L. A., Gruber, F. L., Frankel, A., and Kupfer, S.: Hemodynamic effects of extracorporeal circulation in closed-chest normal animals and in those with myocardial infarction with shock, Circulation Res. 8:199, 1960.
4. Agress, C. M., Rosenberg, M. J., Jacobs, H. I., Binder, M. J., Schneiderman, A., and Clark, W. G.: Protracted shock in the closed-chest dog following coronary embolization with graded microspheres, Am. J. Physiol. 170:536, 1952.
5. Kuhn, L. A., Kline, H. J., Wang, M., Yamaki, T., and Jacobson, J. H., II: Hemodynamic effects of hyperbaric oxygenation in experimental acute myocardial infarction, Circulation Res. 16:499, 1965.
6. Horn, H. D., and Bruns, F. H.: Quant. Bestimmung von L (+)-milchsaure dehydrogenase, Biochem. biophys. acta 21:378, 1956.
7. Huckabee, W. E.: Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and

of hyperventilation, J. Clin. Invest. 37:1244, 1958.
8. Herrmann, G. R.: Experimental heart disease. I. Methods of dividing hearts with sectional and proportional weights and ratios for two hundred normal dogs hearts, Am. Heart J. 1:213, 1925.
9. Gregg, D. E.: Coronary circulation in health and disease, Philadelphia, 1950, Lea & Febiger, Publisher.
10. Moore, R. A.: Coronary arteries of the dog, Am. Heart J. 5:743, 1930.
11. Pianetto, M. B.: The coronary arteries of the dog, Am. Heart J. 18:403, 1939.
12. Smith, H. J., Oriol, A., Morch, J., and McGregor, M.: Hemodynamic studies in cardiogenic shock. Treatment with isoproterenol and metaraminol, Circulation 35:1084, 1967.
13. Fearon, R. E.: Comparison of norepinephrine and isoproterenol in experimental coronary shock. Observations on the effect of dextran infusion, Am. Heart J. 75:634, 1968.
14. Morse, B. W., Danzig, R., and Swan, H. J. C.: Effect of isoproterenol in shock associated with acute myocardial infarction, Circulation 36(Suppl. II):192, 1967 (Abst.)
15. Gunnar, R. M., Loeb, H. S., Pietras, R. J., and Tobin, J. R., Jr.: Ineffectiveness of isoproterenol in shock due to acute myocardial infarction, J. A. M. A. 202:1124, 1967.
16. Cronin, R. F. P.: Effect of isoproterenol and norepinephrine on myocardial function in experimental cardiogenic shock, Am. Heart J. 4:387, 1967.
17. Dietzman, R. H., Lyons, G. W., Bloch, J. H., and Lillehei, R. C.: Relation of cardiac work to survival in cardiogenic shock in dogs, J. A. M. A. 199:825, 1967.
18. Hood, W. B., Jr., McCarthy, B., and Lown, B.: Myocardial infarction following coronary ligation in dogs. Hemodynamic effects of isoproterenol and acetylstrophanthidin, Circulation Res. 21:191, 1967.
19. Hood, W. B., Jr.: Aortic pressure loading in dogs with myocardial infarction, Clin. Res. 15:450, 1967. (Abst.)
20. Hugenholtz, P. G., and Wagner, H. R.: The interaction of the ejection fraction and end-diastolic volume in congenital heart disease during isoproterenol infusion, Am. J. Cardiol. 21:104, 1968. (Abst.)
21. Kuhn, L. A., Kline, H. J., Marano, A. J., Hamby, R. I., Cestero, J., Cohn, L. J., Weinrauch, H., and Berger, M.: Mechanical increase of vascular resistance in experimental myocardial infarction with shock, Circulation Res. 19:1086, 1966.
22. Kuhn, L. A., Kline, H. J., Richmond, S., and Klein, L.: Comparison of the hemodynamic and cardiac metabolic effects of isoproterenol and norepinephrine in experimental acute myocardial infarction with shock, Circulation 36 (Suppl. II):166, 1967. (Abst.)
23. Daniell, H. B., Bagwell, E. E., and Walton, R. P.: Limitation of myocardial function by reduced coronary blood flow during isoproterenol action, Circulation Res. 21:85, 1967.
24. Doerschug, J., and Giaviano, A. A.: Glycogenolysis and phosphorylase activity of cardiac muscle in hemorrhagic shock, Am. J. Physiol. 211:1451, 1966.
25. Greene, H. L., Pitt, B., and Fraenkel, C. C.: Effect of isoproterenol-induced hypotension on regional myocardial blood flow, Clin. Res. 16:231, 1968. (Abst.)

The influence of atrial contraction and mitral valve mechanics on ventricular filling

A study of instantaneous mitral valve flow in vivo

Stanton P. Nolan, M.D.
Sewell H. Dixon, Jr., M.D.
R. Darryl Fisher, M.D.
Andrew G. Morrow, M.D.
Bethesda, Md.

Cardiac performance has been extensively characterized by studies of the hemodynamic events in the left ventricle, a characterization which has been made possible by the development of highly refined techniques for the registration of instantaneous pressures and flow in the ascending aorta and left ventricle. Less attention has been directed to the role of the left atrium, which serves both as an elastic reservoir and as an active booster pump, and in its latter capacity the atrium directly influences ventricular filling and ventricular performance.

A method for measuring and recording the volume and pattern of instantaneous blood flow through the mitral valve was devised and was utilized in the studies to be described. The experiments carried out in normal calves were designed to provide information concerning the atrial contribution to ventricular filling and the mechanical behavior of the mitral valve.

Methods

Calves (68 to 82 kilograms) were studied under halothane anesthesia. During total cardiopulmonary bypass a specially constructed electromagnetic flow transducer (Biotronex Laboratory) was sutured to the wall of the left atrium just above the mitral valve. The transducer was designed as a ring 22 mm. in diameter, and the area of its circular orifice was 3.8 sq. cm. (The mitral annulus in calves of this size is an ellipse with axes of approximately 2.5 and 3.5 cm.) The perimeter of the transducer incorporated a fabric fixation ring through which sutures could be passed, and all blood moving between the atrium and ventricle passed through the orifice of the transducer. The transducer did not distort the mitral valve or obstruct blood flow. An extravascular flow transducer (Biotronex series 3000) was placed on the ascending aorta, and pressures were measured simultaneously in the left atrium, left ventricle, and ascending aorta. All data were recorded simultaneously on magnetic tape (Ampex FR 1300) at 3¾ in. per second and later recorded again photographically (Electronics for Medicine DR-8) for analysis.

The pressure measuring system consisted of semirigid 4 cm. Teflon catheters attached to Statham P23Db pressure transducers driven by Sanborn 350-1100 carrier pre-

From the Clinic of Surgery, National Heart Institute, Bethesda, Md. 20014.
Received for publication Sept. 21, 1968.

amplifiers. The transducers were adjusted to zero pressure at the midpoint of the mitral valve and calibrated against a single column of mercury. The dynamic response of the system was as follows: (1) The frequency amplitude response was linear (± 8 per cent) to 25 cycles per second (c.p.s.). (2) the phase lag was linear with frequency to 15 c.p.s. (3) the transit time varied from 2.8 msec. at 1 c.p.s. to 2.0 msec. at 25 c.p.s. (4) the damping ratio was 0.23.

Instantaneous blood flow was measured using a pulse-logic electromagnetic flowmeter (Biotronex BL-610). The dynamic characteristics of this apparatus were determined in the following way. The magnet drive of the flowmeter and a uniform sine wave of known frequency were passed through a function multiplier. The product of these two signals was led to the input of the flowmeter. The output of the flowmeter was then compared to the original sine wave. This demonstrated that (1) The frequency amplitude response was linear (± 5 per cent) to 50 c.p.s. (2) the phase lag was linear with frequency in this range. (3) the transit time was 4.7 msec. When the dynamic responses of the pressure and flow measuring systems were compared over the range of 1 to 25 c.p.s. it was found that the maximum and minimum differences in transit time were 2.7 and 1.9 msec. respectively.

Seven calves were studied in the anesthetized open-chest state. Continuous recordings were made for periods varying from 1 to 3 hours providing a total of 15 hours of recorded simultaneous pressures and flow. There were spontaneous variations in heart rate from 50 to 200 beats per minute. Cardiac rhythm interpreted from the electrocardiogram ranged from normal sinus rhythm to low nodal rhythm. Cardiac output was maintained between 3,000 and 5,000 ml. per minute and was varied by the slow infusion or withdrawal of blood from the femoral artery. Premature ventricular contractions were produced by light mechanical stimulation of the heart.

Results

Normal mitral valve flow. The normal pattern of instantaneous mitral valve blood flow was determined at heart rates of 70 to

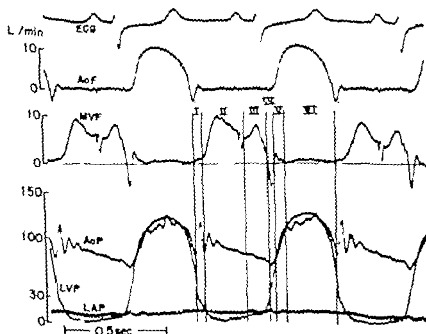


Fig. 1. Simultaneous recordings from a calf with normal aortic and mitral valves. The electrocardiogram (*ECG*) shows normal sinus rhythm and a heart rate of 93. The P-R interval is 0.14 sec. The patterns of aortic (*AoF*) and mitral valve flow (*MVF*) are normal. The aortic (*AoP*), left ventricular (*LVP*), and left atrial pressures (*LAP*) are shown at the bottom. Vertical lines have been constructed to define the six phases of mitral valve flow and each phase is labeled with a Roman numeral (see text).

100 beats per minute and with a P R interval between 0 12 and 0 18 sec. Under these conditions it was possible to define six separate phases of mitral valve flow and their relationships to the atrial and ventricular pressures.

Fig 1 is a reproduction of the simultaneous recordings from one animal studied at a heart rate of 95 *Phase I began simultaneously* with the dicrotic notch of the aortic pressure pulse and was a period of very low rate and volume of flow that lasted 30 to 40 msec during protodiastole *Phase II* began with the onset of the positive atrioventricular pressure gradient flow accelerated rapidly and then declined slowly *Phase III* commenced with atrial contraction when flow again accelerated to a secondary peak and then decreased. Finally with reversal of the atrioventricular pressure gradient flow decelerated rapidly but forward flow persisted for 10 to 15 msec. after reversal of the pressure gradient *Phase IV* was the only period of *reverse flow and thus occurred during isovolumetric* contraction This period lasted 25 to 30 msec. and coincided with the atrial c wave *Phase V* varied in length from 15 to 40 msec It consisted of a small volume and low rate of flow that followed the atrial c wave and was often accompanied by a slight decrease in the atrial pressure. *Phase VI* extended throughout the remainder of systole and during this period there was no detectable forward mitral valve flow

In all animals studied Phases I IV \

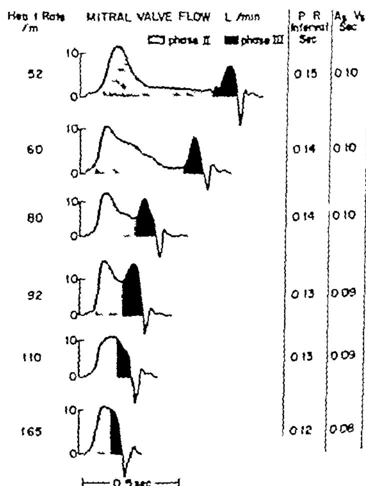


Fig 2 Effect of heart rate on mitral valve flow Mitral valve flow recorded at six different heart rates from 52 to 165 beats per minute The P R and $A_s - V_s$ intervals are normal for each heart rate The area enclosed by Phase II flow is crosshatched while the area under Phase III flow is solid Above heart rate of 92 beats per minute there is no secondary acceleration during Phase III

and VI were similar in amplitude and timing if the mitral valve was competent. Phases II and III however showed marked variations which were related to heart rate and the timing of atrial contraction.

Effect of heart rate. The patterns of mitral valve flow recorded at six different heart rates from 52 to 165 beats per minute are illustrated in Fig. 2. The P R intervals were normal for each heart rate. At rates of 52 and 60 beats per minute little flow occurred during the latter part of Phase II prior to atrial contraction and the onset of Phase III. At rates of 80 and 92 beats per minute there was relatively little decline in Phase II flow prior to atrial contraction and at rates of 110 and 165 the total time for Phase II and Phase III was markedly shortened, and there was no secondary acceleration of flow with atrial contraction.

Timing of atrial contraction. Phase III has been defined as the mitral valve flow during atrial contraction and as expected it varied with the timing of atrial contraction and the P R interval. Fig. 3 presents 5 patterns of mitral flow observed at heart rates between 90 and 95 beats per minute but with progressive decrease in the P R interval. As the P R interval shortened the secondary acceleration of flow decreased in duration and when the interval fell to 0.02 sec. flow also decreased in amplitude. With nodal rhythm there was no flow during Phase III.

Premature ventricular contractions. Premature ventricular contractions occurred spontaneously or were produced mechanically in all animals. The mitral flow patterns observed during these abnormal beats demonstrated a decreased forward volume of flow and the absence of Phase III flow. In some instances Phase IV was 5 to 10

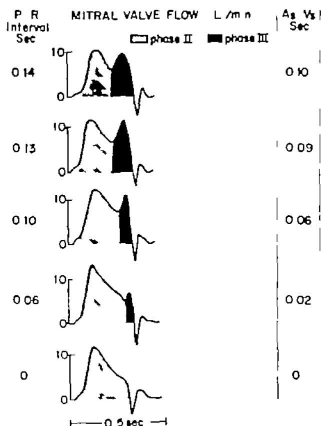


Fig. 3. Five patterns of mitral valve flow recorded at heart rates between 90 and 95 beats per minute but with progressive decrease in the P R interval. The area enclosed by Phase II flow is crosshatched, and the area beneath Phase III flow is solid. As the P R interval shortened, the amplitude and area enclosed by Phase III decreased.

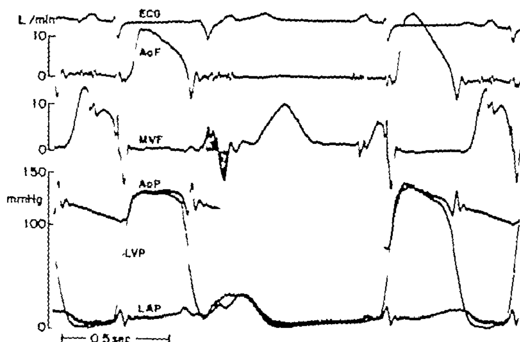


Fig. 4. Simultaneous recordings of the electrocardiogram (*ECG*), aortic flow (*AoF*), mitral valve flow (*MVF*), aortic (*AoP*), left ventricular (*LVP*), and left atrial pressures (*LAP*). A normal heart beat, followed by a single premature ventricular contraction (*PVC*) is shown. The forward and reverse mitral valve flows, preceding the (*PVC*), has been shaded. The width of the negative flow pattern is greater than that of the normal beat, and the negative flow curve encloses a slightly greater area.

msec. longer and enclosed a negative volume of flow 10 to 15 per cent greater than Phase IV of the preceding or succeeding beat (Fig. 4).

Discussion

Passive ventricular filling. Phase II of mitral valve flow is a period of passive ventricular filling determined by the volumes and elastic qualities of the atrium and ventricle. This was thought by Rushmer[1] and Gribbe and associates[2] to be a period of rapid inflow. Although previous investigators have suggested that the succeeding period of diastasis (latter Phase II) represented a marked reduction in the rate of flow, our measurements failed to corroborate such a finding above heart rates of 80. As shown in Fig. 2, the latter part of Phase II flow was markedly reduced at heart rate of 52 and 60 beats per minute, but above heart rates of 80, flow did not fall below 7,000 ml. per minute.

Active ventricular filling. Atrial contraction is known to augment ventricular filling as shown by Mitchell and associates[3] but the proportion of flow during Phase III which results from atrial contraction is difficult to determine. At heart rates of 52 and 60 beats per minute Phase III accounted for approximately 25 per cent of the total flow (Fig. 2). Since flow had fallen to a very low rate during the latter part of Phase II, it can be assumed that the major portion of the Phase III flow was the result of atrial contraction. At the higher heart rates, however, Phase II flow remained high, and even though Phase III accounted for up to 40 per cent of the total flow, it is impossible to infer what percentage of this phase resulted from atrial contraction.

In Fig. 3 the decrease in the duration and amplitude of Phase III with decreasing P-R intervals is obvious, and it is apparent that a properly timed atrial contraction must make a significant contribution to ventricular filling. Gribbe and associates suggested that atrial contraction might augment ventricular stroke volume by 25 to 30 per cent. One animal in our series converted spontaneously from a normal sinus rhythm at a rate of 95 beats per minute to a low nodal rhythm at 98 beats per minute. This provided a unique oppor-

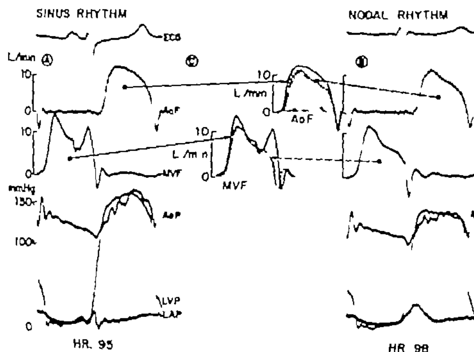


Fig 5. Recordings of aortic flow (AoF), mitral valve flow (MVF), and aortic (AoP), left ventricular (LVP) and left atrial (LAP) pressures obtained during normal sinus rhythm (left) at a heart rate of 95 and nodal rhythm (right) at a heart rate of 98. The recordings were made within 5 minutes of each other in a calf in which the rhythm changed spontaneously. The aortic and mitral valve flow patterns representative of each rhythm are superimposed in the center panel. During nodal rhythm, when there was no effective atrial contraction, MVF and consequently AoF decreased. The difference between the two patterns represents a 20 per cent decrease in stroke volume.

tunity to compare mitral valve flow with and without atrial contraction and the records are reproduced in Fig 5. The loss of Phase III flow during nodal rhythm is apparent, and it was accompanied by a decrease in aortic flow. Thus, in this animal atrial contraction contributed 20 per cent of the total ventricular stroke volume.

Mass acceleration effects. Phase III ends with rapid deceleration of flow to zero. This deceleration begins with reversal of the atrioventricular pressure gradient, but forward flow persists for 15 to 20 msec. thereafter. Spencer and Denison[4] studied ventricular ejection gradients, and noted that during the latter part of systole aortic flow occurred against the pressure gradient. Since Phase III mitral valve flow must decelerate from rates nearly equal to the maximum aortic flow it is probable that the mass acceleration effects found in the aortic root also occur across the mitral valve, resulting in a lag between reversal of the pressure gradient and reversal of the flow.

Mitral valve mechanics. The function of the mitral valve is to allow the unimpeded unidirectional flow of blood from the atrium to the ventricle. The importance of unidirectional flow is based on two assumptions. First, that ventriculoatrial regurgitation during closure of the mitral valve would decrease ventricular stroke volume and efficiency, and second, that regurgitation prior to ventricular contraction would lower the ventricular end-diastolic fiber tension and thereby decrease stroke work. However, information concerning the spatial relationship of the leaflets is not sufficient to demonstrate the presence or absence of regurgitation. It is necessary to determine the instantaneous volume of blood exchanged between atrium and ventricle throughout the cardiac cycle. Phases I, IV and V of the mitral flow recording provide significant information concerning mitral valve mechanics. Phase IV is the only period of reverse flow, and it occurs during initial ventricular contraction. This is caused by the closed mitral valve bulging

into the atrium as ventricular pressure rises Whether or not this is technically mitral regurgitation is debatable. If the blood is beneath the mitral leaflets but displaced to the atrial side of the A V ring it becomes a question of whether the ring or the mitral leaflets represent the demarcation between the atrium and the ventricle. Phase V flow occurs during initial ventricular ejection and although it is a relatively small forward volume of flow it is equivalent to 60 to 80 per cent of the negative Phase IV flow This phase of flow results from the continued contraction of the papillary muscles on the chordae tendineae which draws the mitral leaflets toward the ventricle The overall effect returns the major portion of the Phase IV volume of

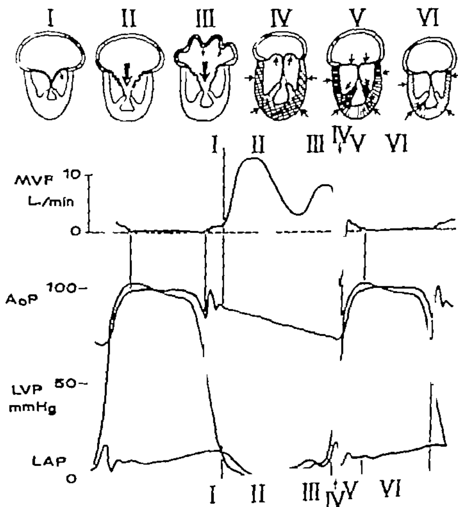


Fig 6 A graphic representation of the six phases of normal mitral valve flow (MVF) and their relationship to the aortic (AoP) left ventricular (LVP), and left atrial pressures (LAP). The behavior of the atrium, ventricle papillary muscles and mitral valve, which account for the changes in mitral valve flow are shown at the top *Phase I* onset simultaneous with dicrotic notch of the aortic pressure pulse. Low rate and volume of flow lasting 30 to 40 msec. during protodiastole As LVP falls, mitral leaflets descend toward the ventricle. *Phase II* onset with positive LAP LVP gradient. Flow accelerates rapidly declines slowly Passive filling of the ventricle determined by the volumes and elastic qualities of the atrium and ventricle. *Phase III* onset with atrial contraction, rising to secondary peak then decelerating rapidly Forward flow persists 10 to 15 msec after reversal of the LAP LVP gradient. This is the only period of active ventricular filling and varies with the timing and force of atrial contraction *Phase IV* the only period of reverse flow This occurs during isovolumetric contraction, coinciding with the atrial c wave. It is caused by the closed mitral leaflets bulging into the atrium as LVP rises. *Phase V* small volume and low rate of forward flow lasting 25 to 30 msec This is caused by continued papillary muscle contraction which draws the mitral leaflets toward the ventricle *Phase VI*: This period extends throughout the remainder of systole. There is no detectable flow until the onset of the succeeding *Phase I*

blood to the ventricular side of the A V septum. In Phase I a small volume of blood is displaced into the ventricle during protodiastole and rapid ventricular relaxation but prior to reversal of the A V pressure gradient. As the ventricular pressure falls, the tension on the mitral leaflets decreases and a volume of blood equivalent to 20 to 40 per cent of the Phase IV (negative flow) volume is returned to the ventricle. The sum of the volumes contained in Phases I and V equals the volume of Phase IV indicating that there is no net ventriculoatrial regurgitation and by inference that there is no true regurgitation of blood between the mitral leaflets with a properly timed atrial contraction. Fig 6 presents a graphic summary of the six phases of mitral flow and their timed relationship to the pressure events.

Premature ventricular contractions Henderson and Johnson[5] believed that mitral regurgitation would result from a ventricular contraction without a preceding atrial contraction, and Friedman and associates[6] reported cineangiographic studies demonstrating mitral regurgitation with premature ventricular contractions. In Fig 4 Phase IV flow of the premature ventricular contraction is wider than normal and encloses a volume 10 per cent greater than the preceding beat. However the difference in the volumes of Phase IV of the normal beat and of the premature ventricular contraction is less than 5 per cent of the normal stroke volume in this animal. It appears, therefore that ventriculoatrial regurgitation can occur prior to mitral valve closure with premature ventricular contractions but that the volume of regurgitation is a small fraction of the expected stroke volume.

In previous studies the effect of atrial contraction in augmenting ventricular filling was not distinguished from its effect in preventing mitral regurgitation. This could explain the disagreement in the literature on the relative importance of each of these effects. From the experiments reported here it is evident that a properly timed atrial contraction is important for optimal ventricular filling and may increase the stroke volume by 20 per cent. On the other hand there was no mitral regurgitation with either sinus or nodal rhythm. Although some regurgitation was noted with premature ventricular contractions the volume was insignificant when compared to the normal stroke volume. The major contribution of atrial contraction to cardiac performance is the augmentation of ventricular filling and not the prevention of mitral regurgitation. The degree to which atrial contraction contributes to ventricular filling depends on the time of its occurrence in the cardiac cycle and on heart rate.

Summary

Instantaneous blood flow across the normal mitral valve was studied in calves. Heart rate and atrial timing varied allowing an assessment of the relative importance of atrial contraction to ventricular filling and to mitral valve closure. Results were (1) The pattern of flow varied with heart rate and P R interval (2) at normal heart rates six phases of mitral valve flow were identified, and they defined the dynamics of the atrium and mitral valve (3) a properly timed atrial contraction can augment ventricular filling by 20 per cent (4) the contribution of atrial contraction to ventricular filling varied with its timing and with heart rate (5) the mitral valve closed without regurgitation during sinus or nodal rhythm (6) premature ventricular contractions could produce mitral regurgitation but the volume was negligible (7) the major role of atrial contraction is the augmentation of left ventricular filling and not the prevention of mitral regurgitation.

REFERENCES

1 Rushmer R. F Cardiovascular dynamics, ed. 2 Philadelphia, 1961 W B Saunders Company.
2 Gribbe P Hirvonen, L. Lind, J and Wegelius C Cineangiocardiographic recordings of the cyclic changes in volume of the left ventricle Cardiologia 34:348, 1959
3. Mitchell, J H., Gilmore J P and Sarnoff S J The transport function of the atrium Factors influencing the relation between mean left atrial pressure and left ventricular end diastolic pressure, Am J Cardiol. 9:237 1962.
4 Spencer M. P and Denison, A. B J The aortic flow probe as related to differential pressure, Circulation Res. 4:476 1956.
5. Henderson Y and Johnson F E. Two of closure of the heart valves, Heart 4:69
6. Friedman, B Daily W M., and Wil Studies on mitral valve function. Ef h ...emia, premature beats a ...s, Circulation Res. 4

Frequency characteristics of some pressure transducer systems

James A. Cronvich, M.S.
George E. Burch, M.D.
New Orleans, La.

Pressure transducers are widely used in cardiovascular studies, such as cardiac catheterization and digital plethysmography, and in other biomedical investigations. Because of the various arrangements of tubing, hypodermic needles, and fluid to couple the transducer to the source of pressure variations, it is desirable to know how accurately the complex pressure wave forms are being recorded. Step function, pulse, and sinusoidal frequency response methods can be used to determine the performance of pressure transducer systems and to predict their performance with complex wave forms. Because the sinusoidal frequency response (amplitude versus frequency characteristic) is used most often as a criterion of system performance and because it was relatively simple to implement, it was used in this study of two commonly used pressure transducers with various diameters and lengths of tubing, with various hypodermic needles, and with air, water, and heparinized blood as coupling fluids.

Method

The arrangement of apparatus shown in Fig. 1 was used to determine the frequency characteristics of the pressure transducers and of the transducer systems.

A small universal motor supplied from the a-c lines through bridge rectifiers was mechanically coupled to drive a model airplane engine as a variable frequency pressure source. The field current of the motor was kept essentially constant, and the armature voltage was adjusted by means of a Variac to vary the speed and give a frequency range of pressure from about 1 to 200 Hz. (cycles per second).

The airplane engine (L. M. Cox Manufacturing Co., Inc., Pee Wee model, 0.020 cubic inch displacement) was one of a pair without intake and exhaust ports, kindly supplied for this study by the manufacturer. As a pump, it generated an almost sinusoidal pressure variation. The amplitude of the pressure variation was determined by the ratio between the system volume and the stroke volume (displacement) of the engine. The cylinder head of the engine was removed and was replaced by a lucite cylinder. The lucite cylinder acted as a storage chamber to prevent excessive system pressures but was small enough not to be self resonant anywhere within the desired frequency range. In

From the Departments of Electrical Engineering and Medicine, Tulane University, New Orleans, La.
Supported by grants from the National Heart Institute of the United States Public Health Service ([illegible]), the Rudolph Matas Memorial Fund for the Kate Prewitt Hem Laboratory, and the Rowell A. Billups Fund for Research in Heart Disease.
Received for publication Nov. 25, 1968.

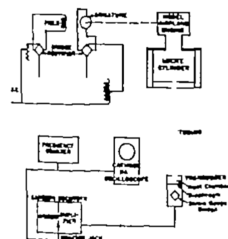


Fig. 1. Diagram of the apparatus used for studying pressure transducer systems.

internal dimensions were length 1 0 in and diameter 1 19 in. One end of the lucite cylinder was cemented to a brass plate which was threaded to screw into the engine cylinder The other end of the lucite cylinder was threaded to screw onto a Statham P23BB transducer The lucite cylinder replaced the regular input chamber of the transducer when the frequency characteristic of the transducer alone was determined. When the systems were studied, the transducer end of the cylinder was closed off by a plastic plug in the center of which was a hole for fittings for attaching tubing or hypodermic needles. Polyethylene and standard white rubber supporter tubings were studied. The polyethylene tubing was Clay-Adams Intramedic tubing sizes PE-10 PE-60 PE-100 and PE 160

Statham type P23BB and type P23Db biomedical pressure transducers were used. A Sanborn Model 301 Carrier Amplifier Recorder recorded the output signal from the transducers. For use above the frequency range of the direct writing section of the recorder a cathode ray oscilloscope was connected to the output of the recorder Frequency was measured with a frequency counter connected to the output of the recorder

Experimental procedure

The frequency characteristics of the recorder and of the recorder plus oscilloscope were determined with a modulated carrier circuit as recommended in the recorder operating manual Where necessary subsequent data were corrected for the high frequency roll-off of the recorder

The temperature of the cylinder the tubing and the input chamber of the transducer was between 70 and 80° F during all tests. Between sets of readings, the air filled systems were opened to the atmosphere therefore, the static pressure in these systems was atmospheric In the liquid filled systems a static pressure above atmospheric was caused by the column of liquid above the transducer therefore, the static pressure varied with the length of tubing However varying the static pressure by varying the vertical distance between the transducer and the lucite cylinder while keeping the tubing length constant showed that over the range used static pressure had negligible effect on the frequency characteristic of the system. The liquid filled systems were always filled with the liquid to a level one-half inch below the top of the lucite cylinder with the space above being air Care was taken to see that the maximum pressure static plus dynamic did not exceed the rated maximum pressure of the transducer

The frequency characteristic of the P23BB transducer was measured with the transducer connected directly to the lucite cylinder The frequency characteristic of the P23Db transducer was measured with a short surgical fitting connecting the lucite cylinder and the input chamber of the transducer

Results

The frequency characteristics of the two transducers with direct air coupling to the pump were quite similar and very nearly flat up to 100 Hz. Consequently as subsequent tests showed the diameter and length of the tubing and needles, the volume of the input chamber of the transducers, and the coupling medium were the important factors affecting the frequency characteristics of the systems studied. Experimentally determined characteristics of some of the systems showing the effects of tubing length and coupling fluid with the P23BB transducer are given in Figs. 2 3 and 4 The needle sizes and the [illegible] hyp-

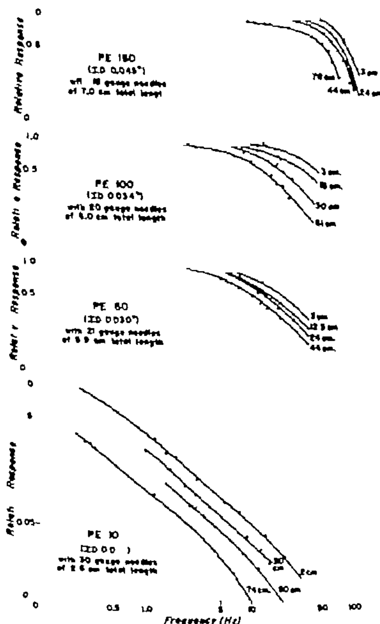


Fig. 2 Frequency characteristics of some air-filled systems. Tubing length are indicated on the curves in this and subsequent figures. Statham type P23BB transducer was used.

dermic needle length used to couple the tubing to the lucite cylinder and to the transducer chamber are indicated in the illustrations.

The effects of needles and of the volume of the input chamber of the P23BB transducer on the cut-off frequency of an air filled system are shown in Fig. 5 (Cut-off frequency is defined as that frequency at which the relative response drops to 0.707 of its value at low frequencies) For equal volumes of input chamber there was little difference between systems using either of the transducers with the same tubing, needles, and fluid. The volume of the chamber of the P23BB transducer was changed with plugs of caulking compound. Although the shape of the plugs affected the frequency characteristics slightly no optimal shape was found.

Discussion

This study shows that *the frequency* characteristics of pressure transducer sys-

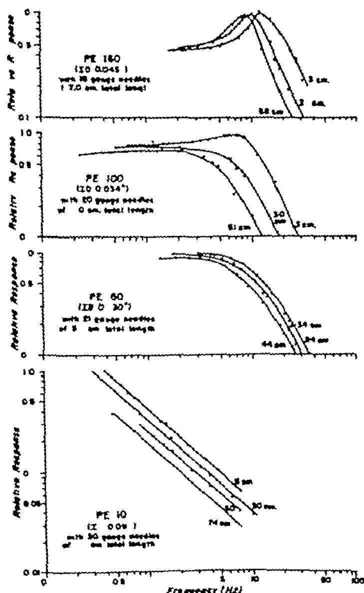


Fig. 3 Frequency characteristics of some ter-filled systems.

tems used in biomedicine are influenced greatly by the internal diameter and length of the tubing and needles, by the volume of the input chamber of the transducer and by the coupl ng fluid. The friction to flow the inertia of the fluid the tubing and needles, and the compliance of the dia phragm of the transducer and of the fluid in the input chamber of the transducer seem to be the factors of most importance. The frequency characteri tics show that some systems have essentially first order characteristics (i.e. the output drops off at the ate of 20 dB per decade increase in frequency above the cut-off f equency) whereas others have essentially second order characteristics (i.e. the output drops off at the ate of 40 dB per decade above the cut-off frequency) In essentially first order systems, friction is more important than the inertia of the fluid in the tubing and needles, and the systems a e highly damped In second order systems, inertia is mportant, and in some cases a reso rise n output is obtained and catir damping.

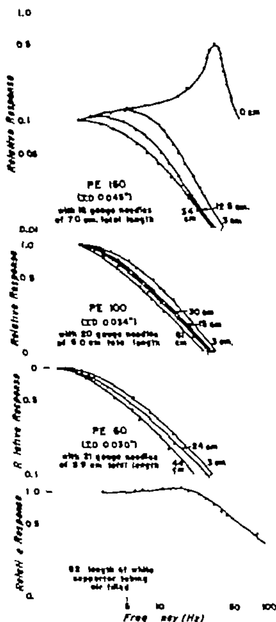


Fig 4 Frequency characteristics of some blood-filled systems and of a long air-filled system.

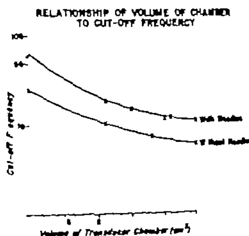


Fig 5 Effects of hypodermic needles and volume of transducer chamber on cut-off frequency of an air-filled system comprising 34 cm. of PE-60 tubing and 5.9 cm. of 21 gauge hypodermic needles.

The air filled systems with PE-10 PE 60 PE 100 and white supporter tubing the water filled systems with PE-10 tubing and the blood filled systems with PE-60 and PE-100 tubing are essentially first order systems. The air filled system with PE-160 tubing the water filled systems with PE-60 PE 100 and PE 160 tubing and the blood filled systems with PE 160 tubing are essentially second order systems.

Because of poor frequency response at frequencies in the range encountered in human pulses (approximately 1 to 10 Hz including the more important harmonics) PE 10 tubing with 30-gauge needles should never be used for pulse pressure recordings.

In digital plethysmography air-filled systems are frequently used and in this laboratory white supporter tubing is used between the finger cup and the transducer. As shown in Fig 4 an 82 inch length of this tubing gives excellent performance up to 30 Hz. with the P23BB transducer. Except for the systems using PE 10 tubing, the water filled systems had second order characteristics, and the frequency characteristics of the larger diameter tubing PE 160 showed severe peaking. For lengths up to 60 cm PE 100 tubing with 20 gauge needles is fairly satisfactory but slightly larger tubing up to perhaps 0 04 in. inside diameter should be better. Care in adjusting inside diameter and length is necessary to avoid either excessive peaking or reduction of bandwidth.

The friction to flow caused by blood viscosity is evident in the blood-filled systems using PE-60 and PE 100 tubing. In general blood-filled systems have poor frequency response. Short lengths of PE 160 (3 to 12.5 cm.) are fairly satisfactory to 8 or 10 Hz. but it is probably better to use water (or saline) filled systems instead of blood filled systems wherever possible to obtain fairly good reproduction of the pulse wave.

Summary

Various air-filled water filled and blood filled pressure transducer systems using different sizes of needles and connecting tubing were studied Using the frequency characteristic as a criterion it was shown that, for optimal reproduction of the human pulse wave, air-filled systems are best. However where liquid filling is necessary water (or saline-) filled systems are to be preferred to blood filled systems.

The efforts of graduate and-ta ts John L. Joynes nd David Ahlgren in this study re ppreciated. Mr Joynes set up the pparatus and conducted most of the tests. M Ahlgren studied the effect of volume of the transducer chamber

REFERENCES

1 Meehan, J P Frequency calibration of sy tems for direct registration of vascular pressures, (air jet siren type of calibrator) Statham Instrument Notes No. 10, July-August, 1949
2. Iberall Arthur S Attenuation of oscillatory pressures on instrument lines, J Res. N t. Burea of Standards 45:85 1950 (Also Statham Instrument Notes No. 22, June, 1952.)

Modified dye dilution technique for cardiac output studies in tiny subjects

René A. Arcilla, M.D.
Marc I. Rowe, M.D.
Chicago, Ill.

Cardiac output estimation by the dye indicator dilution technique is a well established procedure. Indocyanine green dye (Cardiogreen) is commonly used and an arterial dye curve is obtained usually with the aid of a constant rate withdrawal pump. Although the blood is reinfused immediately following the inscription of the curve, the method is not applicable to subjects with very small blood volumes.

This communication describes a modification of the dye dilution technique successfully carried out on newborn puppies, using a Holter pump to withdraw arterial blood into the cuvette and simultaneously reinfuse it back into the subject, thus maintaining constant blood volume.

Materials and methods

Indicator dilution studies were performed on 24 puppies, ranging in weight from 250 to 2,720 grams, using Cardiogreen dye and a Waters XC 302 cuvette densitometer. A Honeywell 1508 Visicorder recorded galvanometer deflections at a paper speed of 10.7 mm. per second. Densitometer response was linear in the range of dye concentrations used. Other physiologic variables recorded were electrocardiogram, rectal temperature, venous pressure, and arterial pressure.

Only local anesthesia was used. Two femoral arteries, two femoral veins, the carotid artery, and the jugular vein were cannulated with small vinyl tubings. The carotid arterial catheter was advanced into the aorta for dye sampling. It was connected to the cuvette densitometer and the latter, to the entrance arm of the Holter pump. The exit arm of the pump was connected to a femoral vein if an arteriovenous (A-V) withdrawal-infusion technique was planned, or to a femoral artery if an arterio-arterial (A-A) withdrawal-infusion technique was desired. The jugular vein catheter was advanced into the superior vena cava for dye injection. The remaining two catheters were connected to Statham pressure transducers for continuous recording of arterial and central venous pressures. A schematic diagram of the catheter-cuvette-pump assembly is shown in Fig. 1. The total volume, from sampling catheter tip to venous or arterial return catheter tip, was 2.5 ml.

In order to minimize pulsatile flow in the cuvette, the revolving stage of the

From the Departments of Pediatrics and Pediatric Surgery, Wyler Children's Hospital, and The University of Chicago, Chicago, Ill. 60637.
Supported in part by grants from the Chicago Heart Association (C66-23) and the National Institutes of Health (HDO 2610).
Received for publication Dec. 12, 1968.
Present address: Division of Pediatric Surgery, University of Miami School of Medicine, Miami, Fla. 33152.

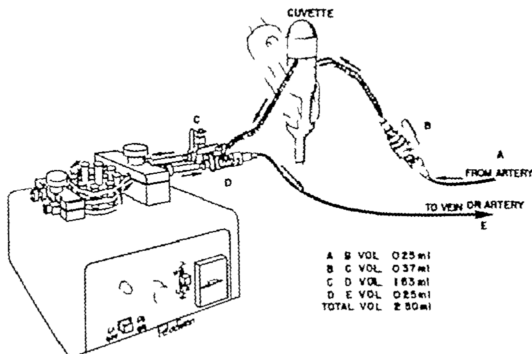


Fig 1 Schematic diagram of Holter pump and cuvett densitometer (continuous circuit sy tem) with corresponding dead space volumes.

pump was modified to contain 9 nstead of the usual 3 rollers. The injection catheter was connected by a three way stopcock to a 20 ml reservoir syringe contain ng the dye solution and to a delivery syringe adjusted to inject a constant volume Preliminary filling of the njection catheter with the dye solution enabled dye injections to be made by volume displacement. After each injection the stopcock remained closed to prevent dye loss from the catheter

The puppy was heparinized at the start of the study Freshly obta ned maternal blood was used to fill the dead space in the cuvette and pump before th dye curve study In this manner the catheter cuvette-pump assembly when n use became an accessory segment of the puppy s circulation After each series of dye curves, blood in the cuvette amounting to 0.4 ml was withdrawn and the cuvette rinsed with saline The w thdrawn blood was then reinfused nto the cuvette before each subsequent dye curve run Blood loss and hemod lution were thus minimized At the end of each tudy the animal was put to death and the blood was collected for dye calibration using at least fou stepwise blood-dye concentrations

In 10 older puppies, weighing more than 1 kilogram each dye curves were also obtained w th the aid of a constant withdrawal Harvard pump for comparison. I a red curves were taken at one to two m nute ntervals and were alternated with those ob ta ned by A V and by A A withdrawal nfusion Cardiac output was calculated by the standard Hamilton method [a] util ng planimetric determination of the primary dye curve area

In 4 of these larger puppies the central aortic blood flow was also determined with n electromagnetic flowmeter The puppies wer anesthetized with Nembutal and connected to a respirator the flow probe was mplanted around the ascending aorta just distal to the coronary orifices A Carol na square wave flowmeter was used and the probe output was fed into an Electronics for Medicine high-gain ampl fier Calibration of the flowmeter was performed *in vit o* by timed passage of a known volume of dog s blood through a fresh aortic segment which was mmersed in a saline bath around which the F had been fitted

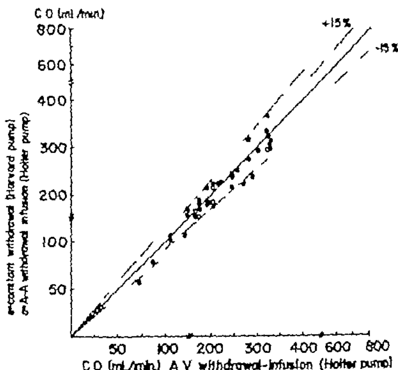
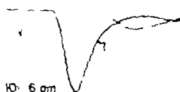


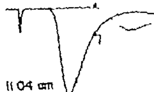
Fig. 2. Comparison of cardiac output values from dye curves obtained by the A-V withdrawal-infusion technique, the V-A withdrawal-infusion technique, and the constant-rate withdrawal method (Harvard pump).

Constant Withdrawal (Harvard Pump)



10:6 am

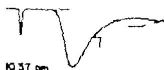
Withdrawal rate 15.3 ml/min
Cardiac Output –
dye curve 273.0 ml/min
flowmeter 277.0 ml/min



11:04 am

Withdrawal rat 24.7 ml/min
Cardiac Output –
dye curve 286.0 ml/min
flowmeter 265.0 ml/min

A-V Withdrawal-Infusion (Holter Pump)



10:37 am

Withdrawal rate 7.5 ml/min
Cardiac Output –
dy curve 74.0 ml/min
flowmete 3 61.0 ml/min



10:53 am

Withdrawal rate 11.2 ml/min
Cardiac Output –
dy curve 339.0 ml/min
flowmeter 337.0 ml/min

Fig. 3. Representative dye curves from a puppy weighing 1.9 kilograms obtained by the A-V withdrawal-infusion technique and by the constant-rat withdrawal method (Harvard pump). Curves in solid lines represent cava-to-proximal aortic dye curves, and those in dotted lines, femoral artery to-proximal aortic curves obtained immediately after the preceding curves and superimposed on the latter to time onset of systemic recirculation (shown by arrow). Simultaneous electromagnetic flowmeter values are also shown.

Results

A total of 201 dye curves were analyzed (109 obtained by the A V withdrawal infusion technique 38 by the A A withdrawal-infusion technique and 54 by the constant-rate withdrawal technique) The curve areas obtained by the A V and A A withdrawal-infusion method were similar and did not differ significantly from those taken in the bigger puppies, with a Harvard pump run at a withdrawal rate of 9.9 ml. per minute The comparative cardiac output values were generally distributed within a ±15 per cent range of identity (Fig 2) The correlation coefficient between the values obtained by the A-V and by the A A withdrawal-infusion methods was +0 99 and the standard deviation of the differences was 10.3 ml. per minute or 4 0 per cent of the mean value obtained by the A V withdrawal-infusion technique. Corresponding data comparing values obtained by the A-V withdrawal-infusion technique at a rate of 9.4 ml. per minute and those of the constant-rate withdrawal method (Harvard pump, 9 9 ml per minute) were r = +0 99 and standard deviation of differences, 41 3 ml per minute or 14 9 per cent of the mean value obtained by the latter method

Femoral artery injection and proximal aortic sampling using the A V withdrawal infusion or the Harvard pump withdrawal method at comparable flow rates demonstrated relatively similar appearance times or systemic circulation times (Fig 3) The cardiac outputs derived from the dye curves also compared closely with those obtained with the aortic flowmeter in larger puppies where the latter determination was made (Fig 4) The correlation coefficient between the flowmeter values and those obtained by the A V withdrawal-infusion technique was +0 99 and the standard deviation of the differences 8.5 per cent of the mean flowmeter values.

The dye curves were highly reproducible Of 54 pairs of dye curves obtained by the A V withdrawal-infusion technique, comparison of the first estimated cardiac output with that obtained 1 to 3 minutes later under the same experimental conditions revealed a standard deviation of

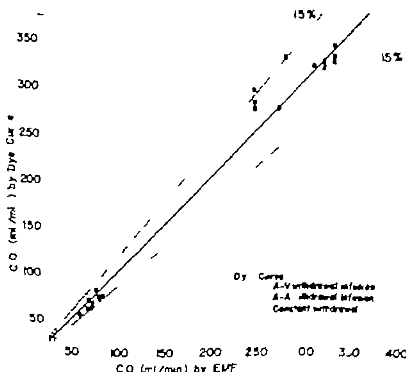


Fig 4 Comparison of dye curve cardiac output values with those obtained simultaneously from an aortic electromagnetic flowmeter

the differences between the two successive determinations of 8 3 ml or 5 2 per cent of the mean output from the first determinations (Fig 5) Corresponding values from 19 pairs obtained by A A withdrawal infusion was 3 7 per cent and that of 27 pairs obtained by constant rate blood withdrawal 3 8 per cent. Both withdrawal infusion methods were well tolerated arterial pressures and cardiac output appeared uninfluenced by the withdrawal rates used (9 4 12 1 and 15 0 ml. per minute) In contrast falling cardiac outputs and declining aortic pressures were often noted when the Harvard pump was used especially in the smaller subjects (Fig 6) This pressure drop appeared to correlate well with the blood withdrawal rates (Fig 7) In four newborn puppies, tolerance to the artificial arteriovenous shunt was tested by running the Holter pump continuously for 1 to 3 hours at a rate of 9 4 ml per minute. This did not produce any serious sequelae Cardiac outputs obtained at intervals varied but not significantl and plasma hemoglobin concentrations remained normal

Discussion

In any hemodynamic investigation, cardiac output estimation is necessary In the case of newborn animals, this is not easily done due to technical difficulties imposed by the small size of the study subjects. Acute flowmeter studies are unphysiologic, and chronic flow probe implantation is difficult. Likewise dye curve cardiac output estimation requiring blood withdrawal by the conventional method, is either not possible or probably unreliable Thus, in the puppies where a Harvard pump was used a tendency for the cardiac output and arterial pressure to fall was generally observed during the inscription of the curves, particularly with increasing withdrawal rates (Figs. 6 and 7) In very young puppies, this blood withdrawal method is not applicable The use of fiber optic catheters would circumvent this difficulty since blood withdrawal is not necessary for the dye curve registration. However the equipment is expensive, and tiny catheters suitable for such small subjects are presently not available.

The present technique utilizing a Holter

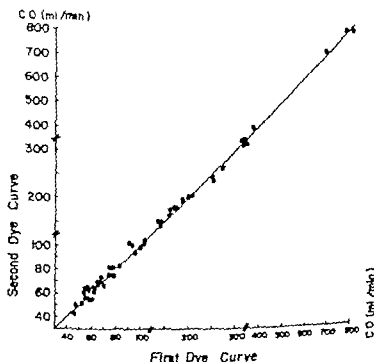
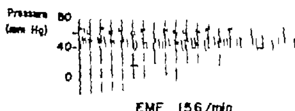


Fig 5 Reproducibility of dye curves by the A V withdrawal infusion technique repeated while 1 t 3 minutes under the same experimental conditions (see text).



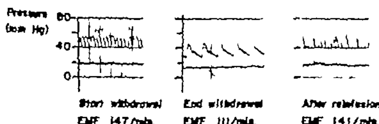


Fig. 6. Change in femoral arterial pressure and in aortic flowmeter output during dye curve inscription, using the A-V withdrawal-infusion technique and the Harvard pump withdrawal technique

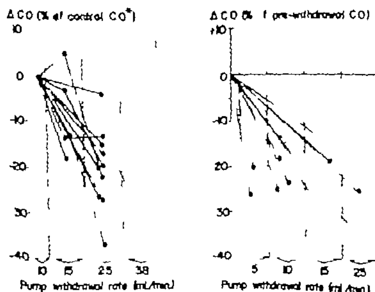


Fig. 7. Changes in cardiac output during dye curve studies on puppies weighing 1.5 to 2.5 kilograms using Harvard pump. Left. Output change at different withdrawal rates expressed in per cent of that obtained ml. per minute withdrawal rate. Right. Actual changes in the flowmeter output during inscription of

pump for simultaneous arterial withdrawal and venous or arterial infusion appears feasible for subjects with small blood volumes. However certain drawbacks must be pointed out. If return flow is into the femoral vein an arteriovenous shunt results. With the usual pump flow rate of 9.4 ml. per minute used in our studies, this shunt flow would correspond to about 10 per cent of the cardiac outputs of puppies weighing 300 grams, and less than 4 per cent of those weighing 1,000 grams or more. Nevertheless, pressure and flow meter recordings of older puppies prior to and during the brief dye curve pump runs have not shown significant hemodynamic changes. This is in contrast to the cardiac output and pressure changes in the puppies in which blood withdrawal was done with a Harvard pump.

The arteriovenous shunt flow via the cuvette and pump results also in dye recirculation separately from that normally occurring in the systemic circulation. However, by avoiding too small a dead space volume of the cuvette-pump assembly or too rapid a withdrawal rate, the pump circulation time remains not rapid enough to critically distort the downslope of the dye curve and cause overestimation of the primary curve area. In failing circulatory states, however, this may not be the case and there is likelihood that cardiac output will be underestimated perhaps even more than what is suspected to occur when the conventional method employing a Harvard pump is used.[4]

It is obvious that the above drawbacks do not pertain to the A-A withdrawal-infusion technique. The latter is indeed ideal for very small subjects. However, it requires additional arterial cannulation. Moreover, the dye curves obtained by this method are generally similar to those obtained with the A-V withdrawal-infusion technique even in the very tiny puppies.

The good correlation between the dye curve cardiac output values and those determined by an electromagnetic flow meter generally agrees with the findings of others.[5-7] However, the latter studies have been conducted on adult dogs, using constant-rate blood withdrawal for the inscription of the dye curves.

The experimental model described seems ideally suitable for hemodynamic investigations in newborn or tiny animals.[8] In addition, the A-V withdrawal-infusion method for performing dye-dilution studies may also be applicable for newborn or tiny infants in which acute blood withdrawal with a Harvard pump may be a likely hazard.

Summary

A modified dye dilution technique for cardiac output estimation in very small subjects is presented. Instead of the conventional constant blood withdrawal technique followed by reinfusion after the inscription of the dye curve, a Holter pump withdraws arterial blood into the cuvette and simultaneously reinfuses it back into the subject's circulation. The results are highly reproducible and compare well with those obtained by the conventional method or by an electromagnetic flowmeter in bigger puppies.

REFERENCES

1. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions, Am. J. Physiol. 99:534, 1932.
2. Hamilton, W. F.: Measurement of the cardiac output, *in* Hamilton, W. F., and Dow, P.: Handbook of physiology, section 2, Circulation, vol. 1, Washington, 1962, Am. Physiol. Soc., p. 551.
3. Hugenholtz, P. G., Gamble, W. J., Moore, R. G., and Polanyi, M.: The use of fiberoptics in clinical cardiac catheterization. II. In vivo dye-dilution curves, Circulation 31:344, 1965.
4. Oriol, A., and McGregor, M.: Indicator-dilution methods in estimation of cardiac output in clinical shock, Am. J. Cardiol. 20:826, 1967.
5. Hamilton, F. N., Minard, J. C., and Schlobohm, R. M.: Measurement of cardiac output by two methods in dogs, J. Appl. Physiol. 22:362, 1967.
6. Malooly, D. A., Donald, D. E., Marshall, H. W., and Wood, E. H.: Assessment of an indicator-dilution technique for quantitating aortic regurgitation by electromagnetic flowmeter, Circulation Res. 12:487, 1963.
7. Camp, F. A., McDonald, K. E., Worman, R., Rekat, A., and Schenk, W. G.: Quantitation of intracardiac shunts, J. Thoracic & Cardiovas. Surg. 47:308, 1964.
8. Rowe, M. I., and Arcilla, R. A.: Hemodynamic adaptation of the newborn to hemorrhage, Pediat. Surg. 3:278, 1968.

An experimental partial occlusive device for vessels delivered by arterial catheter

*Irwin S. Johnsrude, M.D.**
*Jack K. Goodrick, M.D.***
Durham, N. C.

Laboratory investigation of the many dimensions of coronary artery occlusive disease requires experimental models in which varying degrees of occlusion may be applied to specific coronary arteries. A variety of methods have been described in the literature, many of which employ a direct surgical attack on the coronary artery.[1] Catheter techniques have also been used.[2-4] In one of these, a small catheter tip is extruded into the target vessel.[2] We have employed a modification of this approach to introduce specially prepared partial occluding devices (P.O.D.) into any of the three major vessels supplying the heart. The technique has been broadened for use in other visceral vessels. In this manner segmental arterial stenosis has been accomplished at will.

The described technique is clearly an advance beyond the arterial stenosis or occlusion produced by direct surgical approaches. With the catheter technique, the pericardium is not entered, the myocardium is not disrupted (Fig. 1), the adventitia and the media of the coronary artery are not disturbed. The lesions produced by this method are more peripheral in location and smaller in size.

The surgical procedure required is an arteriotomy performed at a remote distance from the heart. This is necessary for introduction of the catheter assembly.

The procedure creates a stenosis, and not an occlusion (Fig. 2). The resulting myocardial ischemia is less sudden in onset and less profound in magnitude. This accounts for a higher survival rate and greater longevity of the experimental animal than if an acute occlusion had been performed. The experimental model more closely simulates conditions producing myocardial ischemia in man.

This technique has been successfully used in 30 young mongrel pigs. With practice the success rate of correctly placing the P.O.D. in a coronary artery approaches 100 per cent. Animal death immediately following or within 24 hours of the P.O.D. placement occurred with an incidence of 40 per cent. This is weighted by our earlier inexperience. Improved techniques have lowered the mortality rate from the initial 65 per cent to a current 33 per cent in the last 18 animals.

Material

The assembled catheter ready to be inserted into the carotid artery has three components (Fig. 3, *B*). It is prepared in

From the Departments of Radiology, Duke University Medical Center, Durham, N. C.
This study was supported in part by Atomic Energy Commission Grant AT-(40-1) 3530 and United States Public Health Grant 309
Received for publication Dec. 1, 1968.
*Division of Vascular Radiology.
**Division of Nuclear Medicine.

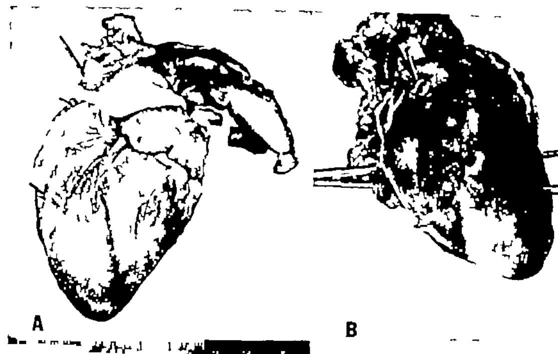


Fig 1 A Anterior view of the pig heart with P O D placed in the anterior descending branch of left coronary artery (see arrow) illustrates the smooth, glistening surface of the heart after 7 days. Note the distal location of the P O D in the coronary vessel. B Right anterior oblique view of the pig heart shows the shaggy fibrinous pericarditis encasing the heart 7 days after thoracotomy for placement of an Ameroid constrictor (see arrow) on the right coronary artery

the following manner The outer 190 polyethylene catheter (inner diameter 1.2 mm and outer diameter 1 7 mm) is preformed by molding with hot water A French no 3 radiopaque Teflon tube with an outer diameter of 9 to 1 0 mm is easily threaded through the polyethylene catheter A slightly longer thin steel wire (outer diameter 0 4 mm) is inserted into the Teflon tubing to temporarily remove the curve from the catheter assembly thus facilitating introduction through the arteriotomy

The P O D is formed of a small strip of lead foil 125 mm thick rolled into a tube having an inner diameter of 9 to 1 0 mm and encased in heat-shrinkable plastic tubing It is then threaded over the inner Teflon core at the distal end of the assembly (c in Fig 3 B) It is held in place by gently heat flaring the end of the Teflon tubing The outer diameter of the P O D may be decreased by omitting the plastic covering Obviously the smaller the outer diameter of the P O D the further it will descend in the preferred artery The level of the lesion within the selected artery may thus be approximated by the choice of outer diameter of the P O D This is in contrast to surgical procedures which must be limited to those areas of the coronary artery which lie in a superficial position and in sufficient length to accommodate the approach

Catheters may be formed with a variety of curves at the distal end. The shape of the curve will depend upon the vessel under investigation on the size and shape of the aortic root and on the preference of the investigator Catheter shapes as seen in Fig 3 B have been found useful by the authors. They have primarily employed the technique of coronary artery catheterization as described by Amplatz and associates[4] (Fig 3 A)

The coronary artery distribution in the pig is very similar to the human coronary artery pattern There are three cusps and three aortic sinuses. There is a noncoronary sinus which lies almost directly posteriorly

*FIT type 105, Alpha Wire Co.

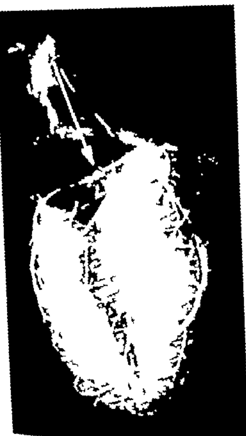


Fig 2 In vitro radiograph following barium-gelatin mixture injection of the pig heart specimen. Note easy visualization of the lead foil P.O D in the right coronary artery

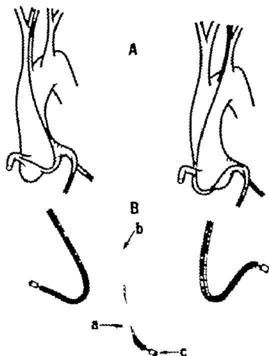


Fig 3 A Line drawing depicts selective position of catheters with attached P O D in coronary ostia. Note either carotid artery may be entered. B Line drawing depicts 3 different catheter configurations and identifies catheter components Outer polyethylene tubing (PE 190 inner diameter 1 2 mm outer diameter 1 7 mm) French no. 3 radio-paque Teflon tubing (b) stretched to an inner diameter of 0 4 mm and an outer diameter of 0 9 mm. P O D ( ) attached over Teflon tubing This device formed from coiled, lead foil 0 125 mm thick, encased in heat-shrinkable tubing has an inner diameter of 0.9 mm and an outer diameter of 2 0 mm

and slightly to the right of the other sinuses. The right coronary ostium arises from its sinus on a plane slightly higher than the ostium to the left coronary artery Thus is at the level of the sinotubular ridge described by Amplatz and co-workers The left coronary ostium arises below the sinotubular ridge in its sinus and almost immediately bifurcates into the circumflex and anterior descending branches. Occasionally these two major left coronary branches may arise from a common ostium in the left coronary sinus. When this occurs the P.O.D can be selectively placed into either the circumflex or the anterior descending branch. Placement of the P O D into the right coronary ostium poses no technical problem.

Procedure

After a common carotid arteriotomy is performed, the catheter is inserted and directed into the ascending aorta under fluoroscopic control The inner steel wire is removed and the preformed curve of the double catheter ensemble with the attached P O D resumes its shape. The tip seeks the orifice of the target vessel and once lodged its position is proved by arterial opacification via contrast injection through the inner Teflon tube (Fig 4 *A* and *B*) The inner Teflon tube is then slowly withdrawn thus dislodging the easily identified lead foil P O D into the vessel Upon removal of the inner Teflon tube a second arteriographic injection through the polyethylene tube confirms the location and patency of the P O D (Fig 4 *C* and *D*) In the majority of these studies, the cine arteriograms taken immediately after place

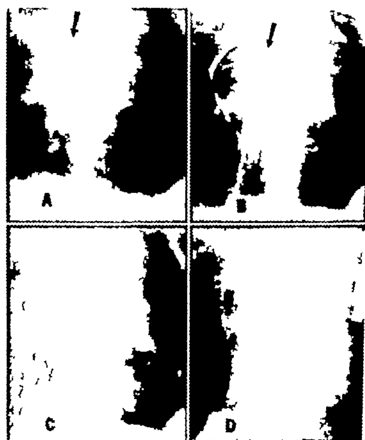


Fig. 4. A. Radiogr ph of selective pos tioning of P O D and the catheter at the right coronary artery ostium. Note ca heter onite ratio optimizes placement. *B* Selective right coronary arteriogram for base line study. C Select right onary rteriogram following dislodgement of P O D Failure of contrast medium to pass beyond I O D ttributed to spasm. *D* Subsequent cinearteriogram after 18 days records persistent patency of P O D

ment record wide patency of the P O D. The authors have observed transient vessel spasm about the I O D in a few cases.

A prime feature of this technique is the capability of establishing base line and immediate post P O D placement arteriograms in a single procedure free of surgical chest morbidity.

Summary

A technique has been described in which experimental stenosis of vessels has been obtained in laboratory animals. A remote catheter technique has been utilized. The advantages of this approach over a direct surgical approach for creating vascular stenotic lesions are listed.

REFERENCES

1. Vineberg, A., Mahanti, B., and Litvak, J.: Experimental gradual coronary artery constriction by Ameroid constrictors, Surgery 47:765, 1960.
2. Gensini, G. G., Palacio, A., Buonanno, C., Kelly, A. E., and Miller, W. F.: Superselective coronary occlusion under cinefluorographic control in experimental animals: Techniques and results, Circulation 31 (Suppl. III) 108, 1964.
3. Hammer, J. and Piao, Z.: A method of isolated gradual occlusion of main branch of a coronary artery in closed-chest dogs, Am. Heart J. 64:67, 1962.
4. Nakhjavan, F. K., Shedrovilsky, H., and Goldberg, H.: Experimental myocardial infarction in dogs. Description of a closed-chest technique, Circulation 38:777, 1968.
5. Amplatz, K., Formanek, G., Stanger, P. and Wilson, W.: Mechanics of selective coronary artery catheterization via femoral approach, Radiology 89:1040, 1967.

Case reports

The angiographic features of a case of parachute mitral valve

Allan L. Simon M D
William F Friedman M D
William C Roberts M D
Baltimore Md

The parachute deformity is an uncommon variant of congenital mitral stenosis, consisting of the insertion of all of the chordae tendineae of the mitral valve into a single, large papillary muscle In the initial description by Shone and associates, and in other reports,[1-4] the anomaly has been most often found as part of a developmental complex consisting of aortic coarctation subaortic stenosis, and supravalvular ring in the left atrium. If diagnosed correctly it is apparent that a corrective operation may be accomplished. In this regard the angiographic appearance of the parachute mitral valve per se has received scant attention although the radiographic features of the associated cardiovascular malformations have been discussed recently[5] A description of the characteristic angiographic appearance of the left ventricular cavity and mitral valve in a well-studied patient with the parachute deformity and a discussion of the mechanism of obstruction to left ventricular outflow in this disorder forms the basis of the present report

Case report

Cyanosis and congestive heart failure ere appeared hortly after the premature birth of J L H (N I H 06-50-00) 4-year-old Caucasian girl She was treated with oxygen nd digitalis and was acyanotic when discharged f om the hospital t 2 months of age Her subsequent course as marked by retarded growth and frequent respiratory infections, and t 1½ ears of age she underwent cardiac catheterization t another instit tion The hemodynamic data (Table I) ere consistent with the diagnosis of valvular pulmonic tenosis and subaortic tenosis. Severe mitral regurgitation was een on left entricular angiocardiogr m. The risk of oper tion was considered prohibit e and the ch ld as discharged from the hospital The next 1½ years were characterized by chronic congestive heart failure and frequent episodes of acut pulmonary edema hich responded initially to increased digitalis, diuretics salt restriction and oxygen. She had become ref actory to these measures and was in pulmonary edema when first eferred and admitted to the N tional Heart Institute

Physical examination revealed a markedly cachectic acyanotic girl (height 87 cm., eight 9 7 kilograms) The chest was barrel shaped and the heart greatly larged. A continuous thrill was promine t at the apex and systolic thrill was palpable in the suprasternal notch Th first nd second heart sounds were single third and fourth heart sounds ere audible at the lower left ternal border A Grade 3/6 systolic jection murmur radiated from the parasternal area at the third interspace int the neck nd back. There was a Grade 4 6 decrescendo holosy tolic murmu nd Grade 3 6 diastolic rumbling murmu t the pex The patient had hypoch omic, microcytic

From the Radiology Department Clinical Center and the Cardiology Branch, Section of Pathology National Heart Institute, National Institutes of Health, Bethesda, Md.
Received for publication March 23 1968
*Present address: Director Cardiovascular Diagnostic Laboratory CMSC-1-169 The Johns Hopkins Hospital, Baltimore, Md. 21205.
Vol 77 No. 6 pp 809-813 June 1969

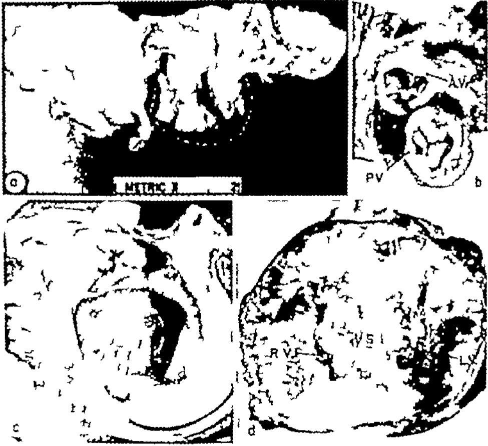


Fig. 1. Opened ... howing only one papillary muscle (enclosed by broken line). The leaflet ... hed ... he ... uscle by very short chordae tendineae. The leaflets are diffusely and irregularly thickened ... deposit. *b*, Intact pulmonic (*PV*) and aortic valves (*AV*). The former is severely stenot... Opened left ... showing thrombus occluding the Kay-Shiley mitral orifice. The left atrial wall ... thickened and the chamber is dilated but no supramitral ring is present. *d*, Transverse section showing that the ... of both ventricles are small. The arrow points to thickened endocardium in the left ventricular outflow tract.

anemia (hemoglobin 8 g ... per cent; hematocrit 26 per cent). The electrocardiogram showed right axis deviation, left atrial enlargement, and right ventricular hypertrophy. Chest roentgenograms demonstrated massive biventricular and left atrial enlargement and pulmonary venous congestion and edema.

The findings at cardiac catheterization are summarized in Table I and, on the basis of the hemodynamic findings, together with the left ventricular angiocardiogram discussed in detail below, the child was referred for operation with the diagnosis of valvular pulmonic stenosis, subaortic stenosis, and parachute deformity of the mitral valve.

At operation the mitral valve was found to be funnel shaped. Instead of normal leaflets there was an extremely thick cone of fibrous tissue with a 4 mm. eccentric orifice. All of the mitral chordae tendineae inserted on a single large papillary muscle which occupied the apex of the left ventricle (Figs. 1, *A* and 2). Endocardial thickening was noted in the left ventricular outflow tract opposite the mitral annulus. The mitral valve and papillary muscle were excised and replaced with a low-profile Kay-Shiley prosthetic valve. ... pulmonary valvotomy was also performed. The hemodynamic measurements determined immediately thereafter are presented in Table I and reveal marked reduction in the gradients across both the pulmonary and subaortic regions compared to the preoperative values. The absence of flow measurements, however, precludes estimation of changes in orifice size.

The postoperative period was characterized by marked respiratory distress and signs of insufficient cardiac output. The patient died 42 hours postoperatively, presumably of dysfunction of the prosthetic mitral valve.

At postmortem examination, the foramen ovale was patent. Both ventricles and the interventricular septum were markedly enlarged. The commissures of a dome-shaped pulmonic valve with small central orifice had been separated at operation (Fig. 1, *B*). A thin membrane of clot over the atrial aspect of the prosthetic mitral disc ... occluded its orifice (Fig. 1, *C*

Table 1. Hemodynamic findings: pressu e in millimeters of mercury

	Igr 2½ yr	Igr 4 y	Intra operative
RAm*	3	7	
RV	130/10	142/6	70/1
MPA	22/10	32/18	21/6
PCW		a 25	
		v 4	
		m 19	
LAm	20		7
LVb	160 —	168/15	95/1
LV	90/—	86/15	
Aorta	90/50	86/42	70/30
LA-LV		9	
Post-PVC pulse pressure		5	

*Abbreviations: RAm, right atrial; RV, right ventricular; MPA, main pulmonary arterial; PCW, pulmonary capillary [illegible] LVb, body of left ventricle; LVo, outflow tract of left ventricle; PVC, premature ventricular contraction.

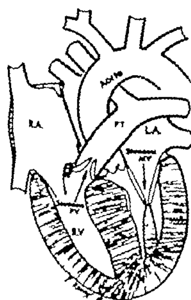


Fig. Diagrammatic representation of the cardiac lesions. The markedly thickened mitral leaflets insert almost directly into the single large papillary muscle at the apex of the left ventricle. Obstruction to left ventricular ejection is caused by restriction of posterior motion of the leaflets which prevent their retraction from the outflow tract during systole and contact between the mitral leaflet and hypertrophied muscular interventricular septum. Mitral regurgitation results from restricted leaflet motion which prevents occlusion of the mitral orifice.

Discussion

In the present patient the hemodynamic determination of pressure gradients across the left and right ventricular outflow tracts and the mitral valve localized 3 sites of obstruction within the heart (Table I). Pulmonic valvular stenosis was clearly demonstrated by the pullback pressure recording across the right ventricular outflow tract, and by a right ventricular angiocardiogram. Mitral and subaortic stenosis were also demonstrated by catheter pullback. The decline in systemic arterial pulse pressure following a premature ventricular contraction suggested that functional rather than fixed orifice obstruction to left ventricular outflow existed at the subvalvular level.

Angiocardiography greatly facilitated the more precise assessment of the lesions responsible for obstruction at both the subaortic and mitral valve levels. Severe deformity of the mitral valve as well as marked thickening of its leaflets was observed in all phases of the cardiac cycle. The diastolic position of the mitral leaflets can be seen in lateral views of the opacified left ventricle (Fig. 3, F); there was restriction of forward motion of the leaflets, leading to a funnel shape. During systole, in addition to the demonstration of mitral regurgitation, there was marked anterior concavity of the anterior mitral leaflet, and the leading edges of both leaflets were seen to be projecting into the left ventricular outflow tract well below the aortic valve (Fig. 3, D). It was apparent that the leading edge of the anterior mitral leaflet formed the posterior component of the obstruction to the left ventricular ejection. A markedly thickened interventricular septum formed the anterior and lateral components of the obstruction. Normally, during systole, the anterior mitral leaflet swings posteriorly out of the outflow portion of the ventricle and meets the posterior mitral leaflet to occlude the mitral orifice so that, in spite of contraction of the muscular interventricular septum, the outflow tract is widened.[7] In the frontal projection during systole (Fig. 3, A) contact between the leading edge of the deformed mitral valve and the anterior bulge of the hypertrophied interventricular septum was visible [illegible]

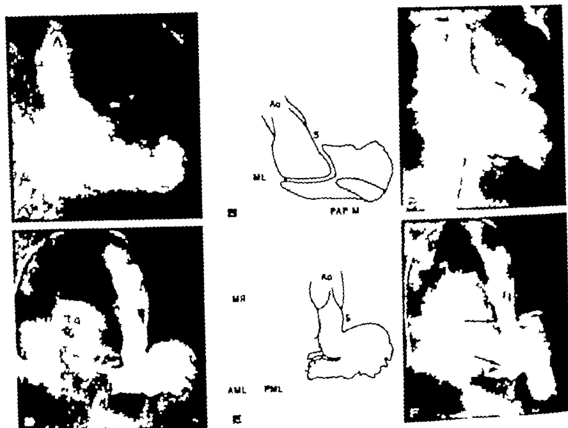


Fig. 3. Left ventricular angiocardiograms and diagram of the contracted ventricle. In the frontal projection after injection (A and B) the hypertrophied muscular interventricular septum (S) can be seen bulging into the lateral aspect of the left ventricular outflow tract. The outflow tract obstruction is visible as a V-shaped radiolucent line formed by the leading edges of the mitral leaflets (ML) as they come in contact with the area of the septal hypertrophy about 2 cm below the opened aortic valve (A). The single large papillary muscle (PAP M) is seen as a radiolucent defect at the apex of the left ventricle. In diastole (C) the septal hypertrophy results in deformity along the inferior surface of the outflow tract. The papillary muscle cannot be delineated, since it is surrounded by a large pool of contrast material. In the lateral projection, after ventricular contraction (D and E) the hypertrophied interventricular septum (S) protrudes into the anterior portion of the outflow tract. The thickened anterior mitral leaflet (AML) and posterior mitral leaflet (PML) are held forward in the outflow tract several centimeters below the aortic valve, forming the posterior component of the subaortic obstruction. Mitral regurgitation (MR) is also demonstrated. There is superimposition of the body and apex of the left ventricle so that the papillary muscle is obscured. In diastole in the lateral projection (F), septal hypertrophy is visible along the anterior aspect of the left ventricular outflow tract, immediately below the aortic valve, and the indentation along the inferior aspect of the ventricle is also caused by hypertrophy of the muscular septum. The interface between the opacified left ventricular blood and less-opacified left atrial blood is formed by the mitral leaflets (arrows) and shows their restricted opening and a funnel deformity.

shaped thick radiolucent line several centimeters below the aortic valve. This location corresponds to the point of pressure change within the ventricle. The normal left ventricular outflow tract shows no such radiolucent defect in systole since the mitral valve moves posteriorly away from the septum.[2]

Although chordae tendineae may not be visualized on a normal left ventricular angiogram, ordinarily two discrete papillary muscles are noted in both the frontal and lateral projections. The anterior muscle may be seen along the anterosuperior surface and the posterior muscle along the posteroinferior surface of the ventricle. Both filling defects were not present in this patient. Rather, only a single large filling defect was seen in an unusual position occupying the cardiac apex (Figs. 2 and 3, A).

It was of particular interest that the dynamics and the appearance of the left ventricular outflow obstruction in this

patient resembled those shown to exist in idiopathic hypertrophic subaortic stenosis (IHSS). In the latter condition the pressure gradient within the body of the left ventricle is thought by some authors to be caused by the abnormal systolic position of the leading edge of the mitral valve leaflets as it contacts the hypertrophied interventricular septum.[7] In IHSS, it is postulated that the abnormal position of these leaflets, which causes mitral regurgitation and subaortic obstruction probably results from traction on the chordae tendineae due to dislocation of the left ventricular papillary muscles by the hypertrophied septum.

In this patient the parachute deformity of the mitral valve (with shortening and fusion of the chordae tendineae as well as fibrosis of the mitral valve) prevents the normal systolic excursion of the mitral leaflets and is responsible for the subaortic stenosis and mitral regurgitation. For this reason the diagnosis of parachute deformity of the mitral valve should be entertained whenever the angiocardiographic association of a single large papillary muscle at the apex coexists with abnormal systolic position of the mitral valve.

REFERENCES

1. Shone, J. D., Sellers, R. D., Anderson, R. C., Adams, P., Jr., Lillehei, C. W., and Edwards, J. E.: The developmental complex of parachute mitral valve, supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta, Am. J. Cardiol. 11:714, 1963.
2. Mehrizi, A., Hutchins, G. M., Wilson, E. F., Breckenridge, J. C., and Rowe, R. D.: Supravalvular mitral stenosis, J. Pediat. 6:1141, 1965.
3. Swan, H., Trapnell, J. M., and Denst, J.: Congenital mitral stenosis and systemic right ventricle with associated pulmonary vascular changes frustrating surgical repair of patent ductus arteriosus and coarctation of the aorta, Am. Heart J. 38:914, 1949.
4. Prado, S., Levy, M., and Varco, R. E.: Successful replacement of parachute mitral valve in a child, Circulation 32:130, 1965.
5. Carey, L. S., Sellers, R. D., and Shone, J. D.: Radiologic findings in the developmental complex of parachute mitral valve, supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta, Radiology 82:1, 1964.
6. Brockenbrough, E. C., Braunwald, E., and Morrow, A. G.: A hemodynamic technic for the detection of hypertrophic subaortic stenosis, Circulation 23:189, 1961.
7. Simon, A. L., Ross, J. J., and Gault, J. H.: The angiographic anatomy of the left ventricle and mitral valve in idiopathic hypertrophic subaortic stenosis, Circulation 36:852, 1967.

Isolated hypertrophic obstruction to right ventricular outflow

Clinical hemodynamic, and angiographic findings before and after operative treatment

Andrew G Morrow M D
R Darryl Fisher M D
Thomas J Fogarty M D
Bethesda Md

Systolic pressure gradients within the *right* ventricular outflow tract are demonstrable in approximately 15 per cent of patients who manifest the typical clinical and hemodynamic features of idiopathic hypertrophic subaortic stenosis (IHSS) When obstruction to right ventricular outflow occurs in such patients, it is usually not severe is of little functional or symptomatic significance and does not necessitate operative treatment. Recently however a child with the familial form of IHSS was shown to have severe and progressive obstruction within the right ventricular outflow tract accompanied by angina pectoris. The clinical and hemodynamic findings in this patient assessed before and after operative treatment are described in the report which follows.

Case report

Clinical summary D P (03-31 79), a schoolboy aged 13 years, was the product of normal gestation and delivery and his growth and development were normal. The diagnosis of IHSS with mild obstruction t *left* entricula outflow was established by cardiac catheterization and angiocardiography in his brother t the age of 7 years. There was no gradient within the right ventricle. The brother died suddenly t eight year of age and the diagnosis of IHSS was confirmed t necropsy

Because of the presence of an jection systolic murmur and the course of his brother the patient wa first studied in 1962 when he was eight years of age. He was asymptomatic, but the electrocardiogram revealed right axis deviation, right ventricular hypertrophy and right ventricular conduction delay (Fig 1). At cardiac catheterization, a peak systolic pressure gradient of 27 mm. Hg was measured within the right ventricular outflow tract in the basal state there was no pressure gradient between the left ventricle and systemic artery.

The patient remained asymptomatic for 3½ years, but t age 12 he had attack of oppressive chest pain while playing football the pain was relieved by rest. Thereafter however precordial pain recurred frequently was precipitated by exercise of decreasing intensity and he was forced to limit his activities to sedentary level. He never experienced syncope or congestive cardiac failure. Because of his symptoms he was again admitted to this Instit te for evaluation.

On examination the child was thin but did not appear ill. The jugular enous pulse exhibited prominent wa and the carotid pulses were brisk. The heart was slightly enlarged t palpation, and a ystolic thrill wa present long the left sternal border nd at the pex. The first and second heart sound were normal, nd the second sound physiologically split. A grade 4/6 jection systolic murmur w audible long the left sternal border and wa transmitted t the base of the heart.

The electrocardiogram again showed right axis

From he Cli ic of Surgery National Heart Insti ute, Bethesda, Md. 20
Received for publication April 15 1968.

 June 1969 Vol. 77 No. 6, pp. 814-81

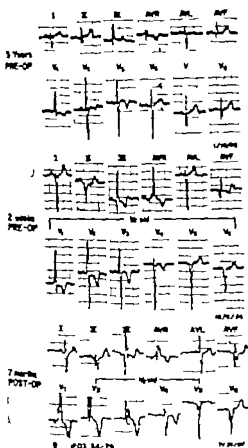


Fig. 1. Electrocardiograms of Patient D. P. recorded five years before operation (top), immediately before operation (middle), and seven months postoperatively (bottom).

deviation, right ventricular conduction defect, and right ventricular hypertrophy (Fig. 1). In comparison to the tracing made five years previously, however, right ventricular hypertrophy was more severe, the Q waves in Leads III and aVF were more prominent, and QS waves were evident in Leads V_1 and V_6. Evidences of right ventricular enlargement were also evident roentgenographically.

Cardiac catheterization revealed no intracardiac shunts, and a systolic gradient of 118 mm. Hg was recorded as the catheter was withdrawn across the outflow tract of the right ventricle. A *selective angiogram* with right ventricular injection revealed thickening and trabeculation of the right ventricular wall and marked hypertrophy of the crista supraventricularis; during systole the outflow tract narrowed strikingly (Fig. 2).

At operation the right ventricle was found to be enlarged, and an infundibular chamber or "third ventricle" was apparent proximal to the pulmonic annulus. A systolic thrill was palpable over the distal outflow tract and main pulmonary artery. A catheter was placed in the proximal right ventricular cavity and another in the pulmonary artery immediately distal to the pulmonary valve. The main pulmonary artery was then gradually constricted with an encircling tape which was placed distal to the pulmonary arterial catheter. As the artery was constricted, the systolic pressure gradient progressively decreased, as illustrated by the recordings of pulmonary arterial and right ventricular pressure reproduced in Fig. 3.

After the institution of cardiopulmonary bypass, a vertical right ventriculotomy was made. The crista supraventricularis and its septal and parietal bands were massively hypertrophied, and these areas were resected. After the septal band of the crista had been removed it was apparent that the interventricular septum itself had a hemispherical appearance and protruded into the outflow tract. The convex portion of the septum was excised and the muscle comprising it was found to be grayish in color and of a somewhat gritty consistency different from the soft, red muscle which made up the crista and its bands. The outflow tract was further enlarged by the insertion of a kite-shaped piece of Teflon fabric into the upper extent of the right ventriculotomy.

Postoperatively the patient's recovery was uneventful, and he returned seven months later for evaluation. He was asymptomatic. A grade 2/6 ejection murmur was audible. The electrocardiogram (Fig. 1) revealed persistent evidence of right ventricular hypertrophy and complete right bundle branch block. At cardiac catheterization the pulmonary arterial and right ventricular pressures were 28/12 and 30/4 mm. Hg respectively. A selective angiocardiogram demonstrated that the outflow tract of the right ventricle was widely patent throughout the cardiac cycle (Fig. 2).

Comment

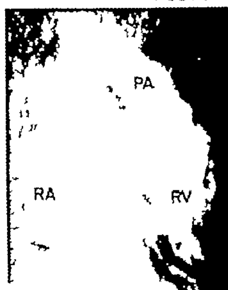
In the patient described, severe obstruction to right ventricular outflow clearly seems to have been an unusual manifestation of the familial form of IHSS. The occurrence of IHSS, with obstruction to left ventricular outflow, had been documented in the patient's brother by cardiac catheterization and angiography, and this diagnosis was later proved at necropsy. In the patient, a progressive increase in the severity of obstruction was suggested by successive electrocardiograms and proved by the data obtained at serial cardiac catheterizations. The dynamic nature of the obstruction was demonstrated by the studies made at operation when the systolic pressure gradient was virtually abolished by an increase in right ventricular afterload (Fig. 3). This hemodynamic sequence has previously been shown to be characteristic of IHSS with either right or left ventricular obstruction. Finally, operative finding of massive hypertrop-

PREOPERATIVE





POSTOPERATIVE



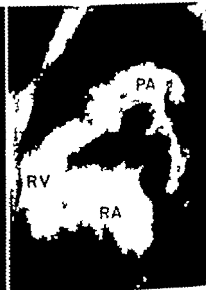


Fig 2 Pre and postoperative selective angiocardiograms, recorded after right ventricular injection, in Patient D P Before operation massive trabeculation of the right ventricular outflow tract is evident in both postero ntero and lateral projections (arrows). Postoperatively the outflow tract remains widely patent throughout the cardiac cycle

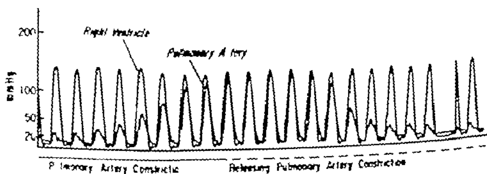


Fig 3 Recordings of pulmonary arterial and right ventricular pressure made at operation. A the pulmonary artery was gradually constricted distal to the site of pressure measurement the systolic gradient was virtually abolished. This response is characteristic of dynamic obstruction t ventricular outflow

of the crista supraventricularis and interventricular septum bore no resemblance to the more familiar entity of discrete subpulmonic stenosis.

One other patient with IHSS and isolated obstruction to right ventricular outflow has been studied in this clinic. At rest a peak systolic gradient of 15 mm Hg was recorded as the catheter was withdrawn across the outflow tract. No gradient was evident within the left ventricle under basal conditions, but with the Valsalva maneuver a systolic gradient of 18 mm Hg between the left ventricle and aorta was provoked. A patient described by Taylor and associates[3] also had severe obstruction caused by a mass of hypertrophic muscle in the outflow tract of the right ventricle and a peak gradient of 78 mm. Hg was recorded at rest there was no gradient between the left ventricle and brachial artery and provocative interventions were not carried out. In this patient, a girl aged 17 years, the obstructing tissue was resected and the operative findings were similar to those in the patient described herein.

It would appear that true, isolated obstruction to right ventricular outflow is extremely unusual in patients with cardiomyopathy. A relatively frequent finding in patients with IHSS, with or without left ventricular outflow obstruction however is the demonstration of an area of abnormally high pressure in the *apex* of the right ventricle. This elevation of pressure results from entrapment of the catheter tip within or between the trabeculae of a hypertrophied ventricle, so-called cavity obliteration, and is not a manifestation of obstruction to flow [2,4,5] Obviously operative treatment would not be indicated or of value in a patient with localized right ventricular hypertension of this type and it may be distinguished from true obstruction at cardiac catheterization. With cavity obliteration an area of low ventricular pressure will be recorded in the inflow area of the ventricle adjacent to the tricuspid valve while the pressure is highest in the inflow tract when hypertrophic muscle obstructs outflow The two entities can also be defined by selective angiography

In the present patient and in the one reported by Taylor and associates, the isolated hypertrophic obstruction within the right ventricle was severe, but in each effective relief of obstruction was achieved at operation and both patients are now free of symptoms. The ultimate courses of these young patients must, however remain in doubt IHSS is recognized to be a process which primarily involves the left ventricle, and the question may be raised as to whether asymmetrical left ventricular hypertrophy may later develop in these patients and lead to recurrent impairment of cardiac performance

Summary

A child is described in whom the familial form of idiopathic hypertrophic cardiomyopathy caused isolated and severe obstruction to right ventricular outflow accompanied by progressive angina pectoris. The obstruction which resulted from massive hypertrophy of the crista supraventricularis and interventricular septum, was treated by resection and prosthetic enlargement of the right ventricular outflow tract. The results of pre and postoperative clinical hemodynamic and angiographic assessments are summarized.

REFERENCES

1 Fra k, S., and Bra wald, E. Idiopathic hypertrophic subaortic stenosis A clinical analysis of 126 patients with emphasis on the natural history Circulation. I press.
2. Pierce, G. E. Morrow A. G and Braunwald, E. Idiopathic hypertrophic subaortic stenosis. III I traoperative studies of the mechanism of obstruction and its hemodynamic consequences, Circulation, Suppl. IV 30 1964
3. Taylor R. R., Bernstein, L., and Jose Obstructi e phenomena in ventricular trophy Brit. Heart J 26 193, 1964.
4 Lockhart, A Charpentier A., J P Ismail, M. B Ourbak, P L. Right ventricular involvement tive cardiomyopathies. Haemod in 13 cases, Brit. Heart J 28
5 Falcone, D M Moore E. C Idiopathic hypertrop involving the right ventr 19 735 1967

Tricuspid candida endocarditis complicating a permanently implanted transvenous pacemaker

John M Davis M D
Arthur J Moss M.D **
Eric A Schenk M D
Rochester N Y

Implantation of a permanent transvenous pacemaker has become an accepted procedure for the treatment of symptomatic complete heart block. As with most new procedures, complications are inevitable and ventricular perforation cardiac arrhythmias,[2] and sepsis[3] have been described One complication rightfully anticipated but unreported to date is tricuspid endocarditis complicating implantable transvenous pacemakers. The following case is believed to be the first report of tricuspid candida endocarditis associated with a permanently implanted pacemaker

Case report

Clinical summary A 71 ear-old man with diabetes mellitu entered the Newark W yne Community Hospital on Aug 8 1966 with diffuse bdominal pain His pa t history revealed two syncopal episodes during the preceding year On dmission, the heart rate was 36 beats per minute d the blood pressure was 180/70 mm. Hg The veins were not distended and the lungs were The heart w not enlarged, heart sound istant the intensity of S_1 was variable nd re no heart murmurs The liver nd spleen felt, nd there was no peripheral edema. cardiograms revealed complete heart block with a slow idioventricular rhythm. A temporary transvenous pacemaker was inserted on Aug 17 1966, and the patient was transferred t the Strong Memorial Hospital where a permanent transvenous pacemaker† wa implanted on Aug 19 1966. The battery was implanted subcutaneously in the left pectoral region, and the catheter was inserted into the right ventricular apex v the left external jugular ein. Threshold for pacing was 1 5 milliamps, the generator output was set t 5 milliamps, and effective pacing wa established t a rate of 76 beats per minute The temporary pacemaker wa removed Procaine penicillin, methicillin, and kanamycin tibiotics were administered for three days. The postimplant course was uncomplicated, nd the patient as discharged on the fifteenth hospital day ith blood pressure of 150/90 mm Hg

Two weeks later a transurethral prost tic resection was performed because of obstructive urologic symptoms. A Foley catheter was not required, but intermittent courses of broad spectrum antibiotics were administered for the treatment of recurrent urinary tract infections.

During the next nine months the patient was rehospitalized on three occasions with severe congestive heart f ilure. Serial chest roentgenograms revealed progressive cardiomegaly Digitalis and diuretic therapy were instit ted. Throughout this period proper pacemaker function was documented by electrocardiography On his final hospitalization on M y 15 1967 the patient was febrile and confused, the blood pressure was 106/70 mm. Hg, and

om the Departments of Medicine and Pathology University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital, Rochester N Y
ved for publication June 16, 1968
ding Physician, Newark Wayne Community Hospital, Newark, N Y
st for reprints should be addressed Arthur J Moss, M D 260 Crittenden Blvd Rochester N Y 1462

† Mfg. Medtronic, Inc Minneapolis Pulse Generator Model 5 70-C; Catheter Electrode, Model 5814;

[illegible]



Fig. 1 Autopsy examination of the heart and transvenous pacemaker with the right-sided chambers exposed. A large right atrial vegetation has formed about the catheter and it partially obstructs the tricuspid valve. See text for details.



Fig. Low-power view of section of (RA), tricuspid valve (TV), and (RV). The dark [illegible] atrial and tricuspid valve vegetation [illegible] specific [illegible] (Methenamine silver [illegible])



Fig 3 Tricuspid valve vegetation containing candida organisms with both hyphal and yeast forms. (Methenamine silver stain ×250.)

mmation was present both in the subendocardial area and on the luminal surface of the vegetations. A small area within the right atrial vegetation consisted of hemosiderin-laden macrophages and showed evidence of organization. Multiple microabscesses containing candida organisms were present in the myocardium and kidney. Most of these were adjacent to or associated with small blood vessels which contained thrombotic material and candida organisms within their lumina. A large pulmonary abscess consisted of necrotic debris, inflammatory cells, and candida organisms.

Discussion

The first case of mycotic tricuspid endocarditis complicating an implanted transvenous catheter is presented. Large mycotic vegetations were attached to the right atrial wall, partially obstructed and involved the tricuspid valve, and extended into the inferior vena cava. Documentation of candida as the offending organism in the endocarditis was ascertained from the morphologic features of the vegetations on microscopic examination. The tricuspid valve as well as the large right atrial vegetations contained both hyphal and yeast forms of the candida organisms. Andriole and associates[4] in their comprehensive review of candida endocarditis have accepted microscopic descriptions of this as adequate evidence for the diagnosis. Further supporting data of the systemic dissemination of the organism in[...] positive throat and urine culture organisms during the terminal [...]on fungal organisms on direct [...] the pulmonary suppuration [...]d the presence of mycelial hyphae in the histologic sections of myocardium, lung, and kidney. The absence of positive blood cultures in patients with candida endocarditis has been reported previously.[4]

Unfortunately, the specific species of candida was not identified in the present case. The portal of entry of the candida organism may have been related to the original pacemaker implantation procedure ten months prior to death or possibly to the transurethral resection performed a few weeks after pacemaker insertion. The patient had a number of predisposing factors classically associated with mycotic endocarditis.[4,6] He was diabetic, received broad-spectrum antibiotics during pacemaker implantation, and was treated with several courses of antibiotics for repeated urinary tract infections. In addition, the transvenous catheter electrode was a foreign body, and it may have damaged the tricuspid leaflets as they repeatedly closed against it. Finally, the patient was chronically ill with debilitating coronary heart disease.

Mycotic endocarditis was first described in 1915 with systemic blastomycosis,[7] and involvement of the right atrium with blastomycosis was reported in 1937.[8] Candida endocarditis was first reported in a morphine addict who injected infected solutions of heroin intravenously,[9] and since then monilial endocarditis has been described in a wide variety of clinical settings.[4,6,10,11] Almost all the reported cases of candida endocarditis have involved the left side of the heart, and the authors are aware of only four previous reports of candida endocarditis involving the tricuspid valve.[11,12] The most recent report of tricuspid candida endocarditis was associated with embolization of a 30 cm polyethylene catheter to the right side of the heart one year earlier.[12] The bulky mycotic vegetations which formed about the catheter partially obstructed the tricuspid valve, and many features of that case are similar to our report.

One of the characteristic features of candida endocarditis is the large size of the atrial vegetations,[4,6] and the present case is no exception. The 2 by 2 cm vegetation partially obstructed the tricuspid valve, and it may have contributed to the

patient's progressive and intractable congestive heart failure. The clinical recognition of obstructive atrial vegetations requires a high index of suspicion. Jugular venous distention and prominent "a" waves may be difficult to evaluate if the jugular veins have been used for catheter insertion. Tricuspid murmurs may develop though they were not evident in the present case. Definitive recognition of obstructing atrial vegetations during life will require angiocardiography.

The premortem recognition of candida endocarditis may be difficult in view of the paucity of positive blood cultures on routine study.[6] Unexplained fever in the presence of a permanently implanted pacemaker catheter should suggest the possibility of a fungus endocarditis. Special blood cultures utilizing Sabouraud's media should be obtained in suspected cases. In addition the catheter should be removed and cultured if the sepsis persists. Once the diagnosis of candida endocarditis is established aggressive therapy is required. Intravenous administration of amphotericin B the recommended drug of choice is usually not effective in eradicating the infection since large vegetations are generally the rule.[6] Surgical removal of the infective nidus is required.[12] Open-heart surgery should be performed to remove the large vegetations, and possibly to replace the involved tricuspid valve with a prosthesis. The transvenous pacemaker system should be replaced by a transthoracic unit with implanted epicardial electrodes at the time of the open heart surgery.

Summary

The first reported case of tricuspid candida endocarditis which developed in association with a permanently implanted transvenous pacemaker is described. The patient died ten months after pacemaker implantation and his terminal illness was characterized by congestive heart failure, fever, leukocytosis, and seven negative blood cultures. At autopsy a large monilial vegetation was attached to the right atrial wall, involved and partially obstructed the tricuspid valve and extended into the inferior vena cava. Histologic examination of the vegetations, the heart, the lung, and the kidney revealed the presence of candida organisms.

The authors are indebted to Dr. William J. Welch who performed the autopsy examination at the Newark Wayne Community Hospital, and thank Miss Cynthia Stebbins for her secretarial assistance.

REFERENCES

1. Moss, A. J., and Rivers, R.: Myocardial perforation by a permanent transvenous pacemaker, New England J. Med. 2?3:265, 1966.
2. Bluestone, R., Davis, G., Harris, A., Leatham, A., and Siddons, H.: Long-term endocardial pacing for heart block, Lancet 2:307, 1965.
3. Lagergren, H., Johansson, L., Landegren, J., and Edhag, O.: One hundred cases of treatment for Adams-Stokes syndrome with permanent intravenous pacemaker, J. Thoracic & Cardiovas. Surg. 50:710, 1965.
4. Siddons, H., and Sowton, E.: Cardiac pacemakers, Springfield, Ill., 1967, Charles C Thomas, Publisher.
5. Andriole, V. T., Kravetz, H. M., Roberts, W. C., and Utz, J. P.: Candida endocarditis: clinical and pathologic studies, Am. J. Med. 32:251, 1962.
6. Merchant, R. K., Louria, D. B., Geisler, P. H., Edgcomb, J. H., and Utz, J. P.: Fungal endocarditis—review of the literature and report of three cases, Ann. Int. Med. 48:242, 1958.
7. Hurley, T. D.: A unique lesion of the heart in systemic blastomycosis, J. M. Res. 33:499, 1915.
8. Baker, R. D., and Brian, E. W.: Blastomycosis of the heart, Am. J. Path. 13:139, 1937.
9. Joachim, H., and Polayes, S. H.: Subacute endocarditis and systemic mycosis, J. A. M. A. 115:205, 1940.
10. Henderson, J., and Nickerson, J. F.: Bacterial endocarditis with candida albicans superinfection, Canad. M. A. J. 90:452, 1964.
11. Jamshidi, A., Pope, R. H., and Friedman, N. H.: Fungal endocarditis complicating cardiac surgery, Arch. Int. Med. 112:370, 1963.
12. Kay, J. H., Bernstein, S., Feinstein, D., and Biddle, M.: Surgical cure of candida albicans endocarditis with open-heart surgery, New England J. Med. 264:907, 1961.
13. Henderson, J., and Nickerson, J. F.: Bacterial endocarditis with candida albicans superinfection, Canad. M. A. J. 90:452, 1964.
14. Fraser, R. S., Rodman, F. S. B., and MacGregor, J.: Candida endocarditis in the right atrium following successful treatment of subacute bacterial endocarditis of the mitral valve, Acta cardiol. 21:491, 1966.
15. Wellman, K. F., Reinhard, A., and Salazar, E. P.: Polyethylene catheter embolism, Circulation 37:380, 1968.

Clinical pathologic conference

*Cecil A Krikower M.D**
*Irving Friedman M.D ***
*Roger A Harvey M D ***
Chicago Ill

History

This 40-yea -old Caucasian housewif was ad mitted to the Research and Educational Hospitals on Nov 18, 1967 following transfer from another hospit l in th state. She had had episodes of pa n- f l knees without welling which subsided in one t ts da s thout the se of medication over the past year Early in October 1967 some five weeks before admission, she noted the sudden onset of pain in both knees w th welling which subsided on aspirin therapy W th this last episode she lso developed painf l swelling of both ankles and the formation of black bullous lesions over both lateral malleol She claimed she had used Omega oil on her knees, b t did not think she had used it on her nkles. She did use moist heat before the ppearance of the lesions The painful swelling in the ankles persisted and teroid therapy was instituted although the dose was unknown. She was hospitalized on Oct. 23 1967 because of increased pain nd welling and enlargement of the blood-f lled vesicular lesions over the ankles. Signs of phlebitis in the right leg were present nd shortly after admission she developed signs suggestive of pulmonary en bolism Heparin wa started and the pleuritic chest pa gradually subsided.

Laboratory findings during hospitalization in October were Hemoglobin 8 8 Gm hematocrit 31 per cent, sed mentation rate 32, white blood count 11 700 to 22 000, with 75 per cent neutrophils, 21 per cent ly phocytes, 2 per cent eosinophils, and 1 per cent basophils. Blood glucose was 198 mg per cent, total protein was 8.2 Gm. per cent th gamma globulin 2 16 Gm. per cent, β-globulin 1.8 Gm. per cent, α-globulin was 1 14 Gm. per and α-globulin was 0.71 Gm. per cent. Po- m measured 6 mEq per liter sodium was q. per liter Carbon dioxide measured 22.3 measured 83 mEq per liter antistreptoly sin-O t ter wa 833 The serologic test for syphilis was nonreactive The agglutination test for the rheumatoid factor was weakly positive Coombs tes was negative, as were two lupus erythematosus preparations. Because of the development of signs of thrombophlebitis i the left leg nd lack of specific diagnosis, she was tr nsferred t this hospital

Physical examination The patient was very obese lethargic, and ppeared t be acutely ill The temperature was 98.8° respiration was 24 nd shallow pulse wa 100 and blood pressure measured 114/70. The fund showed some rteriolar narrowing The head and neck examination was otherwise normal. Examination of the chest revealed bilateral expiratory wheezes and right-sided les. The point of maximum impulse wa estimated t be about 15 cm. from the midsternal line in the fifth intercostal space Third and fourth sound were present. There was a grade II/VI systolic ejection murmur along the left lower sternal border The spleen as not felt nd the liver edge was not palpable but there wa f llness and tenderness for four fingerbreadths below the right costal margin. Pelvic examination was normal. The most triking findings were in both legs. Pitting edema was present to both inguinal ligaments. The skin wa tender hen touched. The skin of both feet was described as dusky or cyanotic. There was a 10 cm. ulcer with a necrotic base and a ll-defined border present over the left lateral malleolus. A smaller but similar one was present on the right. There wa no effusion l to the joints. N pulses were felt in either leg

Initial hospital course. Shortly after admission, the patient blood pressure became unobtainable This responded w thin four hours to the prompt administration of hydrocortisone and plasma. Because of change in both the examination and electrocardiogram, it was felt that this episode was precipit ted by another bout of pulmonary em-

From the Departments of Pathology and Radiology University of Illinoi College of Medicine, and he Department of Medicine, Chicago Medical School, Chicago, Ill
Received for publication June 21 1968.
*Reprint request to C. A. Krikower, M.D., Department of Pathology University of Illinois College of Medicine 1853 W Polk St., Chicago, Ill. 60612.
**From the Department of Medicine, Chicago Medical School, Chicago, Ill
***From the Department of Radiology University of Illinoi College of Medicine Chicago, Ill

bolism, and heparin was begun (75 mg intravenously every four hours). Over the next four days the blood urea nitrogen rose from 45 to 100 mg per cent. The urine output was less than 500 c.c. per day. On the fifth hospital day the urine output rose to 4,000 c.c. and continued at this level for three days. Laboratory findings Nov. 18 through Nov. 27 were as follows: Hemoglobin 9 Gm., hematocrit 29 per cent, reticulocytes 7.5 to 11.5 per cent, platelets 62,000 dropping to 22,000, white blood cells 37,000 dropping to 13,200 with 76 to 84 per cent segmented forms, 3 to 1 per cent myelocytes, 7 to 10 per cent lymphocytes, 5 to 6 per cent monocytes, and 20 nucleated red blood cells per 100 white blood cells. Four per cent helmet and fragmented red blood cells were seen. Bone marrow aspiration showed erythroid hyperplasia, but no iron stores. Megakaryocytes were present. Urinalysis showed the following: Albumin 1+, 10 to 15 white blood cells and 3 to 6 red blood cells per high-power field. There were few granular but no red blood cell casts. Blood chemistries revealed the following results: Sodium 108 to 122 mEq. per liter, potassium 5.4 to 6.2 mEq. per liter, chlorides 68 to 83 mEq. per liter, carbon dioxide 15 to 21 mEq. per liter, blood urea nitrogen 45 to 92 mg. per cent, creatinine 2.1 to 2.9 mg. per cent, uric acid 13.5 mg. per cent, calcium 4.3 mEq. per liter, fasting blood sugar 180 mg. per cent, alkaline phosphatase 51 King-Armstrong units, inorganic phosphorus 4.1 mg. per cent, serum lactic dehydrogenase 1,050 units (24 per cent heat labile, 28 per cent heat stable), serum glutamic oxaloacetic transaminase 432 units, total bilirubin 0.9 mg. per cent (direct 0.2 mg. per cent), cholesterol 187 mg. per cent, total protein 6.6 mg. per cent with 23 per cent gamma globulin, 14.9 per cent beta globulin, 12.2 per cent alpha₂ globulin, 10.4 per cent alpha₁ globulin; 39.9 per cent albumin, serum iron 14 micrograms per cent, total iron binding capacity 361 micrograms per cent. The venereal disease research laboratory test was nonreactive. No lupus erythematosus cells were present. The latex fixation test was nonreactive. The antistreptolysin-O titer was 833 units. The status of clotting mechanism on Nov. 22 was: fibrinogen 100 mg. per cent (normal 200 to 400), partial thromboplastin time 47 sec. (normal 30 to 45), thrombin time 13 sec. (normal 27), factor VIII 91 per cent (normal 50 to 150). Chest film on Nov. 20 showed normal cardiac configuration. Electrocardiogram (ECG) on Nov. 18 at 9:00 P.M. showed: Rate 112, P-R interval 0.16 sec.

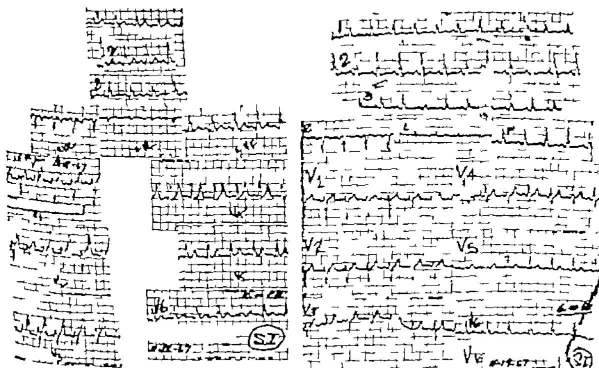


Fig. 1 *Fig. 2*

Fig. 1. ECG at 10:00 P.M. Nov. 18, 1967. Rate 106, P-R 0.16 sec., QRS 0.155 sec. T waves of iliac prolongation of leftward type. R and T waves in right precordial leads consistent with right ventricular hypertrophy and/or true posterior wall myocardial infarct.

Fig. 2. ECG at 6:40 P.M. Nov. 19, 1967. Rate 108, P-R 0.14 sec., QRS 0.11 sec. T waves ... R waves in V... Flat T waves in III, AVL. Nonspecific T-wave changes and intraventricular

phenomena detailed in the first two phases or whether this was a continuation and complication of lupus. The interesting therapeutic point in this regard is that when heparin was increased there was definite improvement in the platelet count and the levels of the coagulation factors. Also her BUN and other chemistries seemed to have improved including the alkaline phosphatase which came down to 22 King Armstrong units. However both legs became more gangrenous.

This leads us to the fifth and final phase in which she developed large subdural hematomas which had to be evacuated bilaterally. Although she regained some degree of consciousness after surgery she did not respond and died. Now we know that the platelet count was normal about this time, so that this must have happened during the period of severe thrombocytopenia and defibrination.

In attempting to tie the first four phases into the total clinical picture I cannot help but think that the infarctive vascular lesions were primarily due to involvement of the venous system with some effect on arterial sufficiency and that these were based on some type of hypersensitivity syndrome, especially lupus erythematosus, even though the LE preparations were negative and there was only a slightly positive rheumatoid agglutination test. Supporting the diagnosis of lupus, we would include the low total serum complement, the increased gamma globulin and the previous history of pain in the knees for some time. In making this diagnostic assumption, we would have to consider whether or not there is any relationship between lupus disseminated intravascular coagulation and thrombotic thrombocytopenic purpura (TTP). Dr McKay[4] has considered TTP as being part of the syndrome of disseminated intravascular coagulation and he believes that this occurs in lupus. However others like Lerner and associates[5] clearly separate TTP from disseminated intravascular thrombosis and the generalized Shwartzman phenomenon. As to the relationship between ... and TTP much has been written ... con. Levine and Shearn[3] point ... there may be a subpopulation of TTP which includes patients with classical features of lupus namely an increased incidence in women more frequent biological false positive serologic reactions, elevated serum globulins, splenomegaly arthralgias, arthritis, and pleuritis. I think that most of us have seen both of these types of patients viz. TTP without lupus and TTP with lupus.

My feeling in this case is that we are dealing with an atypical form of lupus erythematosus which developed the vascular complications as I described went through an episode of massive intravascular coagulation similar to TTP and unfortunately did not respond adequately because of the subdural hematomata.

DR. HARVEY Three portable AP film examinations of the chest were made. The first on Nov 20 showed well-expanded lungs with no infiltrates and no signs of pleural involvement. The central vasculature was normal. The second film was taken at 1.30 P.M. Dec. 13 and showed areas of soft increase in density in the right upper left lower and to a lesser extent right lower lung fields. Central vascular shadows were now considerably increased. The heart was not unduly prominent. The third film at 9.30 P.M. Dec. 13 showed progression of the densities in the lung fields involved previously. There were new areas of density as well. The picture was that of multiple pulmonary infarcts.

DR. KRAKOWER At autopsy there were widespread cutaneous ecchymoses and petechiae. There was pitting edema of both legs extending to the thighs. Both feet were gangrenous. The serosal cavities were free of fluid. The heart weighed 320 grams. The right atrium was small. There was endocardial roughening over several pectinate muscles which microscopically proved to be recent thrombi made up of platelets and fibrin. The right ventricle was somewhat enlarged measuring 9.5 cm. from the ring of the tricuspid valve to the apex, and 10.5 cm from the apex to the pulmonary valve. The circumference of the pulmonary conus was 10.5 cm. The trabeculae were thickened as was the mural myocardium which measured 0.6 cm in thickness at the origin of the inflow tract and 0.65 cm in the distal portion of the outflow tract. There were several atheromatous plaques in the main pulmonary

artery There were no thrombi or emboli The left side of the heart was not remarkable, except that there was some ventricular hypertrophy and thickening of the cusps of the aortic valve with considerable calcific atheromatous deposits in the sinuses. Microscopically there was a film of fibrin with polymorphonuclears adherent to the ventricular surface of one cusp. There were no bacterial colonies. There were some atheromatous plaques in the coronary arteries without significant luminal narrowing There was appreciable atherosclerotic involvement of the arch of the aorta and more than the expected amount in relation to the intercostal vessels of the thoracic aorta. The lungs were very heavy the right weighing 1 050 and the left 995 grams. There were fibrinous patches over the serosa in places, while in most areas there was older vascularized edematous fibrous pleural thickening There was an extensive pneumonic process involving all lobes of both lungs with microscopically serous, serofibrinous and seropurulent exudate. There was a large hemorrhagic and partially suppurative infarct involving the left lower lobe measuring 8 by 5 cm There were multiple recent and older organizing and organized thromboemboli in the main and distal pulmonary arterial branches to the right and left lower lobes. In addition there were microscopically many bone marrow emboli in small pulmonary arterial branches and even in the canalized channels of organizing thromboemboli.

In the abdomen the principal findings were those related to arterial and venous thromboses. Of the systemic veins, both common iliacs and both right and left internal and external iliac veins were completely thrombosed. In addition several veins in the broad ligaments and the left renal vein for its full length were thrombosed As in the pulmonary arteries the microscopic examination of these veins revealed varied stages of organization of the thrombi. There were sectors with little or no organization varying to sectors with well-advanced organization. In the portal system there was a recent thrombus, partially filling the hilar portion of the portal vein over an area 2.5 by 1.5 cm., with extension into and occlusion of the branch to the left lobe of the liver There was also a recent thrombus 1 cm long occluding the hilar portion of the splenic vein. On the arterial side there was a massive thrombus occupying most of the length of the abdominal aorta (Fig 3) This thrombus occluded the lumen of the aorta from the level of the renal arteries to the bifurcation It extended superiorly to occlude the right renal artery It surrounded but did not occlude the superior mesenteric artery but it did occlude the celiac axis There was propagation of the thrombus from the celiac axis to the proximal portions of the left gastric hepatic, and splenic arteries There were marked ulcerative atherosclerotic lesions of the abdominal aorta underlying the thrombus. Microscopically there was at best minimal organization of these arterial thrombi As a result of both arterial and venous thromboses, the liver revealed a massive anemic softened infarct of the left lobe measuring 4 by 5 cm (Fig 4) The organ was otherwise enlarged weighed 2 050 grams, and presented marked acute passive congestion The spleen was enlarged weighing 400 grams with two extensive softened and partly liquefied mahogany red infarcts (Fig 5) The one at the superior pole measured 9 0 by 6 5 cm The one at the inferior pole measured 3 5 by 3 0 cm. The



Fig 3 Thrombos[illegible] of abdominal ... of the thrombus above the re... the celiac axis and encroach... the superior mesent... ...nd below the ren... of the right renal ... dominal aorta.

vagus nerves do not innervate the ventricular muscle. Whether or not increased activity in vagus nerves has a negative inotropic effect on the ventricle is in dispute.[11,18] However, recently in this laboratory we have shown that in the dog there is only a negligible inotropic response e.g. stimulation of the vagus nerves which resulted in decrease of heart rate of more than 100 beats per minute caused only a 5 per cent reduction in peak ventricular pressure and dP/dt max at constant heart rate.[19]

It is well known that an increased concentration of catecholamines in the blood or activity in sympathetic nerves to the heart result in a positive inotropic response.[7,8] Using the method described above as a means of quantitating the inotropic response and infusing isoprenaline, adrenaline and noradrenaline each at several different rates, it has recently been shown that the increases in inotropic response were proportional to the increases in heart rate but the rise in inotropic response was proportionally greater during the infusion of l noradrenaline (Fig. 2). It is known that the action of the noradrenaline is reduced because noradrenaline is taken up into the sympathetic nerve endings; isoprenaline is not taken up.[20] By blocking the uptake of noradrenaline with cocaine hydrochloride it was shown that though there was no change in the response to isoprenaline the responses to l noradrenaline were changed so that both dose-response relationships and the relative chronotropic and inotropic effects were the same as isoprenaline.[21] It was concluded that the explanation of the difference in responses of the heart to isoprenaline and noradrenaline is that l-noradrenaline is taken up into the sympathetic nerve endings in the S-A node and in the muscle and there is a greater uptake of l noradrenaline in the region of the S-A node than in the muscle of the left ventricle.

Stimulation of the right ansa subclavia is known to give a qualitatively different response from stimulating the left (for references, see Levy and associates[22]). Again using our technique of assessment of the inotropic response of the ventricle the effects of stimulation of the right and left ansae subclaviae in the dog were assessed quantitatively. A diagram illustrating the responses is shown in Fig. 3. Stimulation of the right cardiac sympathetic nerves is associated with a large increase in heart rate and a small positive inotropic effect

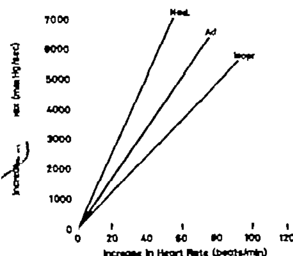


Fig. 2. Diagram of a comparison of inotropic responses to increasing rates of infusion of noradrenaline, adrenaline, and isoprenaline. At each dose of each catecholamine, the positive inotropic response (y-axis), measured at the same paced heart rate throughout the run, is compared with the response of the free heart rate (x-axis) obtained at that dose. (From Linden, Furnival, and Snow, unpublished work.)

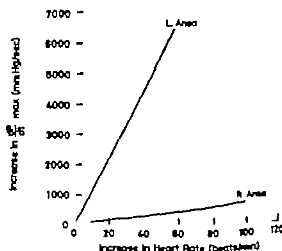


Fig. 3. Diagram of a comparison between stimulation of the right and left ansae subclaviae. At each frequency of stimulation the positive inotropic response (y-axis), measured at the same paced heart rate throughout the run, is compared with the response of the free heart rate (x-axis) obtained at the same frequency of stimulation. (From Linden, Furnival, and Snow, unpublished work.)

but stimulation of the left sympathetic nerves results in a relatively greater inotropic response.[22] These effects were observed in both the right and left ventricles. One explanation is that the sinoatrial node receives more sympathetic nerve fibers from the right ansa subclavia than the left.[23]

It is now clearly evident that these mechanisms may be recognized in the intact animal and human heart it is apparent that the force of ventricular contraction in addition to being affected by the Frank Starling mechanism is altered by the concentration of catecholamines in the blood and by the activity in sympathetic nerves to the heart.[24] However it is not possible to assess the relative importance of each of these factors in controlling the contraction of the ventricle particularly at rest and during mild exercise but from studies in man and animals undergoing severe exercise t is possible to conclude that both activity in sympathetic nerves and an increase in the concentration of circulating catecholamines are necessary for the performance of maximum exercise and to infer that similar mechanisms are involved in mild to moderate exercise. It is also possible to suggest that about half the change in stroke volume of the ventricle in severe exercise is attributable to the Starling mechanism and about a quarter to each of the increases in circulating catecholamine and activity in sympathetic nerves. As with many other physiological mechanisms, the absence of one or other of these sympathetic effects reduces only little the capacity of the animal for maximum work. The absence of both sympathetic effects leaves the heart to increase ts force of contraction solely through the Frank Starling mechanism and there is then considerable reduction in the attainable maximum exercise.[24]

It is therefore possible to speculate on the mechanisms involved in the function of the transplanted heart. After the heart has been transplanted the Starling mechanism will immediately be available. The concentration of catecholamines in the circulating blood will presumably change although it is probable that not all the stimuli which evoke the response are known. Some nerves will reconnect to the heart muscle provided enough of the atria are retained and little of the posterior mediastinum is disturbed evidence has been given that some nerves regrow to a reimplanted dog heart within 4 weeks of transplantation and that within 1 to 3 years almost full normal nervous function of the heart is obtained.[24,25] Thus a transplanted heart may have available to it most of the efferent mechanisms necessary to adjust to the changes in cardiac output.

This discussion has taken into consideration only the responses of the heart to increased activity in the efferent nerves to the heart. The significance of the afferent nerves from the heart has not been discussed. It has been known for some time[27,28] that receptors exist at the junctions of the pulmonary veins and left atria and that these receptors increase their discharge in response to stretching of the walls.[29] Though it is known that an increase in discharge of these receptors into the vagus nerves causes an increased urine flow[30] the efferent limb of this response is unknown. This response does not involve the antidiuretic hormone[31] there is, as yet, no evidence that this mechanism plays a part in the regulation of blood volume.

However recently a new reflex has been described in which stimulation of these same left atrial receptors, found at the pulmonary vein-left atrial junctions caused an increase in heart rate the afferent nerves of the reflex were solely in the vagus nerves and the efferent nerves solely in the sympathetic nerves to the heart.[32-34] Surprisingly this reflex has been shown not to have any positive inotropic effect on the ventricles.[35] Though this reflex has been observed in dogs and the significance in man is unknown it is possible to speculate that its importance may be that t regulates the size of the heart to within very narrow limits. Because (1) the time of ventricular systole, and thus the time of the filling of the left atrium during this period is relatively constant, and (2) receptors respond in the main to a rate of change of deformation during this period it is suggested that this reflex by increasing the heart rate in response to an increased rate of inflow into the left atrium during ventricular systole, maintains the volumes of the heart relatively constant du
increased flow of blood t
ring the increased

Thus an increased inflow into the left atrium would cause an increased rate of change of pressure in the atrium during ventricular systole an increased rate of discharge of the atrial receptors and an increased heart rate This increase in heart rate reduces the time of filling of the ventricle leading to a smaller ventricle than would have obtained without the reflex Though this is speculation it may indicate that enough of the left atrium of the recipient should be retained so that the receptors at the pulmonary vein atrial junctions and as many afferent nerves as possible are included

Three facts suggest that it would be best to join the donor heart to the superior and inferior venae cavae (1) scar tissue between the recipient part of right atrium and the donor part of right atrium (if the join is made at the right atrium) may prevent the conduction of the impulse e.g the function of the transplanted sinoatrial node has been found to be unpredictable[34] apparently because of scar tissue (2) almost normal efferent nervous function of the transplanted heart is eventually attained (see above) (3) the function of the right atrial receptors is at the moment unknown and there is always the possibility that their afferent nerves will reconnect

In conclusion it seems that the nerves to the heart are necessary for normal function that the nerves to the transplanted heart eventually regain their function and that possibly the best junction of the venous systems is to connect the donor heart at the superior and inferior venae cavae and the left atrium

Some of this work was completed with the help the Wellcome Trust the British Heart Foundation and the Medical Research Council.

REFERENCES

Webb W R Howard H S and Neely W A Practical method of homologous cardiac transplantation, J Thoracic Surg 37:361 1959

Goldberg M Berman E F and Akman, L C. Homologous transplantation of the canine heart, J Internat. Coll. Surgeons 29:575 1958

3 Lower R R Stofer R. C., and Shumway N E. Homovital transplantation of the heart J Thoracic & Cardiovas Surg 41 196, 1961

4 Shumway N E., Angell, W W and Wuerflein R D Progress in transplantation of the heart. Transplantation 5:900 1967

5 Dubost P C., and Cachera, J P La greffe allogenique du coeur chez l'homme, Presse méd 6 1651 1968

6 Sarnoff S J and Mitchell, J H The control of the function of the heart, Hamilton W F editor Handbook of physiology section 2, Circulation, vol 1 Washington 1962 American Physiological Society p. 489

7 Linden R. J The control of the output of the heart, in Creese R. editor Recent advances in physiology ed 8 London, 1963 J & A Churchill, Ltd p 330.

8. Linden R. J The heart ventricular function, Anaesthesia 23:566, 1968.

9. Katz, L N Symposium on the regulation of the performance of the heart, Physiol. Rev 35:90, 1955.

10 Eichna, L W and McQuarrie D G Symposium on central nervous system control of circulation Physiol. Rev 40 Suppl. 4 part II 1960.

11 Leonard E and Hajdu, S. Action of electrolytes and drugs on the contractile mechanism of the cardiac muscle cell Hamilton, W F editor Handbook of physiology section 2, Circulation vol 1 Washington 1962 American Physiological Society p 151

12. Bowditch, H P Uber die Eigenthumlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen Ber Konigl Sachs Ges Wissen 23:652 1871

13. Sonnenblick, E H Force velocity relations in mammalian heart muscle Am J Physiol 202:931 1962

14. Woodbury J W Cellular electrophysiology of the heart, Hamilton W F editor Handbook of physiology section 2 Circulation, vol 1 Washington, American Physiological Society 1962, p. 237

15 Brockman, S. K. Dynamic function of atrial contraction in regulation of cardiac performance Am J Physiol 204:597 1963

16 Bayliss W M and Starling E H On some points in the innervation of the mammalian heart, J Physiol 13:407 1892

17 Sarnoff S. J Brockman, S. K Gilmore J P Linden, R. J., and Mitchell J H Regulation of ventricular contraction Influence of cardiac sympathetic and vagal nerve stimulation on atrial and ventricular dynamics Circulation Res 8 1108, 1960.

18. DeGeest, H Levy M N Zieske H and Lipman, R J Depression of ventricular contractility by stimulation of vagus nerves, Circulation Res. 17:222, 1965

19 Furnival C. M Linden R J and Snow H M : The response of the left ventricle to stimulation of the vagus nerves J Physiol 198 100P 1968

20 Burgen, A. S. V and Iversen L. L. The inhibition of noradrenaline uptake by sympathomimetic amines in the rat isolated heart, Brit J Pharmacol. 25 34 1965

21 Furnival C. M Linden R. J and Snow H M : Chronotropic and inotropic effect of isoprenaline and L-noradrenaline in the dog heart J Physiol. 196 109P 1968

22. Levy M N Ng M L and Zieske H Func

tional distribution of the peripheral cardiac sympathetic pathways. Circulation Res. 19:650 1966.

21. Furnival, C. M., Linden, R. J., and Snow, H. M.: Response to stimulation of the cardiac sympathetic nerves, J. Physiol. 197: 74P 1968.

22. Donald, D. E., Ferguson, D. A., and Milburn, S. E.: Effect of beta-adrenergic receptor blockade on racing performance of greyhound with normal and denervated hearts, Circulation Res. 22:127 1968.

23. Peiss, C. N., Cooper, T., Willman, V. L., and Randall, W. C.: Circulatory responses to electrical and reflex activation of the nervous system after cardiac denervation, Circulation Res. 19:153 1966.

24. Dong, E., Jr., Hurley, E. J., Lower, R. R., and Shumway, N. E.: Performance of the heart two years after autotransplantation, Surgery 56:270, 1964.

25. Nonidez, J. F.: Identification of the receptor areas in the venae cavae and pulmonary veins which initiate reflex cardiac acceleration (Bainbridge reflex), Am. J. Anat. 61:203 1937.

26. Miller, M. R., and Kasahara, M.: Studies of nerve endings in the heart, Am. J. Anat. 115:217 1964.

27. Coleridge, J. C. G., Hemingway, A., Holmes, R. L., and Linden, R. J.: The location of atrial receptors in the dog: physiological and histological study, J. Physiol. 136:174 1957.

30. Ledsome, J. R., and Linden, R. J.: The role of left atrial receptors in the diuretic response to left atrial distension, J. Physiol. 198:15 1968.

31. Ledsome, J. R., Linden, R. J., and O'Connor, W. J.: The mechanism by which distension of the left atrium produces diuresis in anesthetized dogs, J. Physiol. 159:87 1961.

32. Ledsome, J. R., and Linden, R. J.: A reflex increase in heart rate from distension of the pulmonary vein atrial junction, J. Physiol. 170:456 1964.

33. Ledsome, J. R., and Linden, R. J.: The effect of distending a pouch of the left atrium on the heart rate, J. Physiol. 193:121 1967.

34. Kidd, C., Ledsome, J. R., and Linden, R. J.: Left atrial receptors and the heart, J. Physiol. 185:78P 1966.

35. Furnival, C. M., Linden, R. J., and Snow, H. M.: The response of the heart to stimulation of left atrial receptors, J. Physiol. 198:75P 1968.

36. Ernst, R. W.: Transplantation of the sino-auricular node to the right ventricle for the treatment of complete heart block, Ann. New York Acad. Sc. 111:869 1964.

Treatment of pulmonary embolism

Arthur C DeGraff Jr M.D
Charles A Bucknam M D
Hartford Conn

The lung is a vascular sieve Its principle circulation lies in series with the systemic circulation so that in the absence of vascular anomalies, virtually all blood returning from systemic veins to systemic arteries must pass through the capillaries of the lung Thus all particles arising in systemic veins of size too great to permit passage through capillaries are removed from the blood impacting on lung blood vessels rather than in vessels of vital organs supplied by the systemic circulation The lung is well adapted to its function as a vascular sieve since it is both endowed with a double circulation which insures supply of vital nutrients should one source of blood supply be obstructed and contains within its substance an abundance of materials such as fibrinolysins, lipase and macrophages, necessary for clearing blood vessels of impacted material The efficiency with which these naturally present systems work has been well demonstrated by the experimental work of Springate and associates,[1] showing clearing of 90 per cent of small autologous clot emboli from rabbit lungs within 4 hours, and by the clinical observations of Fred and associates[2] showing clearing of even lobar artery emboli within 10 days.

Pathophysiology and supportive therapy

Pulmonary hypertension which results from pulmonary emboli is most frequently due to mechanical block of blood vessels by embolized material In the presence of massive pulmonary embolism causing severe increase in pulmonary arterial pressure, precapillary arteriovenous anastomoses may open allowing systemic venous blood direct entry into the systemic arterial circulation with a resulting fall in arterial oxygen saturation. Since increased cardiac output is necessary to provide tissue oxygenation when arterial blood is deficient in oxygen and since arterial hypoxia may cause pulmonary arterial constriction oxygen should be administered when arterial hypoxia is demonstrated

Bronchi serving the embolized area of the lung constrict either secondary to the release of serotonin from agglutinations of platelets contained in or formed on embolized material or due to the effect of reduced carbon dioxide concentration in the airways and blood vessels of the lung supplied by the blocked vessels. This bronchoconstriction in the area of obstructed blood flow acts to reduce dead space ventilation and is, therefore desirable. Occasionally generalized bronchoconstriction may occur or pulmonary hypertension may develop out of proportion to the mechanical block of blood vessels. These events may be reversed in part by isoproterenol administered systemically or by aerosol

In the presence of severe pulmonary hypertension the right ventricle may fail to

From Departments of Medicine and Surgery Hartford Hospital, Hartford, Conn and Department of Medicine Yale Medical School, New Haven, Conn.
Address requests for reprints to: Arthur C DeGraff, Jr. M.D 85 Jefferson St., Hartford, Conn. 06106.
*Clinical Assistant Professor of Medicine, Yale Medical School.

maintain adequate cardiac output, with resultant shock. Routine measures to counteract shock and heart failure, such as digitalis and vasopressors, should be employed in this situation.

Etiology

If materials foreign to the body are excluded pulmonary emboli will result from (1) Clot emboli (Fragmentation of clot formed on the damaged walls of systemic veins, the heart, or pulmonary arteries reinstitution of blood flow in systemic veins, where blood flow has been interrupted for a sufficient time for clotting to occur) (2) septic embolism (3) conversion of fibrinogen to fibrin in systemic veins by action of bacterial endotoxin amniotic fluid or other substances (fibrin emboli) (4) introduction of fat globules into systemic circulation following trauma (fat emboli)

Diagnosis and treatment

Clot embolism

DIAGNOSIS Treatment of pulmonary embolism requires accurate diagnosis of the extent, cause, and site of the embolism When clot emboli are suspected on clinical grounds, their presence can be proven only by angiographic techniques Lung scanning remains a useful tool to exclude the diagnosis of pulmonary emboli since although defects shown on a lung scan can result from many diseases, a normal lung scan is never seen in the presence of angiographically proven pulmonary emboli. Measurement of the carbon dioxide gradient between end tidal air and arterial blood is particularly valuable as a confirming screening test for massive life threatening pulmonary embolism while preparations are made for angiography and a team is assembled for possible surgical removal of the lung clot. End tidal P_{CO_2} should be less than 50 per cent of arterial P_{CO_2} for the diagnosis of massive pulmonary embolism to be entertained

MEDICAL TREATMENT Anticoagulant therapy by heparin injected intravenously in a dose sufficient to maintain the clotting time greater than 30 minutes before the next dose (usually 40 000 U of heparin per day) is generally conceded to be the treatment of choice to prevent formation of new clots or propagation of old clots. This dose is based on experimental evidence that clots do not propagate at this level of anticoagulation. By proper use of heparin not only should further emboli be prevented but also it should not be possible for a new clot to be formed on an embolized clot. The recommended duration of heparin therapy is still disputed Ideally heparin therapy should be continued until (1) maximal clearing of the pulmonary vascular defects has been achieved and (2) inflammation of the source of the embolism has cleared and the surface of the clot has epithelized Since the source of embolism is usually not known and repeat pulmonary angiograms are not routinely performed in most institutions, the duration of heparin therapy is usually arbitrarily decided. The average recommended duration of therapy is 3 weeks, although recommendations range from 3 days (with continued anticoagulation with warfarin) to 3 months. While heparin therapy clearly stops propagation of clots, such results do not occur with warfarin or coumarin compounds. Therefore during the acute period following embolism (the first 3 weeks) therapy should be with intravenous heparin alone. Intravenous heparin can be administered conveniently through the self-sealing stopper of an indwelling scalp vein catheter which need be changed only every 48 hours. Heparin cannot be used for long term anticoagulant therapy because of its undesirable metabolic side effects (i.e. skeletal decalcification) and because of inconvenience for outpatient management. For these reasons, warfarin therapy is usually begun after 3 weeks of heparin therapy The efficacy of substances which prevent platelet agglutination such as dipyridamole or glycerol guacolate, has not yet been established in long term trial. Until such information is available recommendations regarding use of these drugs must be deferred.

Since there normally exist adequate mechanisms for removing clots from the lung therapy of pulmonary clot embolism should be directed to prevent further emboli except where a life threatening emergency requires immediate su[...] tervention. There is only sugge[...] dence that infused fibrinolysins

kinase and urokinase) increase the speed of lysis of clots in patient's lungs and there is no evidence that the end result achieved by infusion of fibrinolysins is in any way better than that which is achieved by the body's natural mechanisms for removing clots.

SURGICAL TREATMENT. *Venous interruption* is indicated in the following situations to prevent *recurrent major pulmonary* embolism: (1) following massive embolism attended by transient shock, (2) recurrent embolism in the face of adequate heparin anticoagulation or recurrent embolism when anticoagulation is contraindicated, (3) septic embolism. We emphasize that the diagnosis must be confirmed by angiography or an unambiguous lung scan. In most cases, interruption of the inferior vena cava is the treatment of choice. In relatively uncommon instances, unilateral leg disease may be well documented clinically and by bilateral phlebography, in which case interruption of the superficial femoral vein may be the better procedure. The application of a serrated plastic clip to the vena cava immediately below a good-sized lumbar vein is the preferred technique. Miles and Taber and their associates[3,4] have reported that clipping effectively prevents emboli without production of a pressure gradient. About one third of these will develop thrombosis of the clipped area, but there is a lower incidence of postoperative edema and iliofemoral thrombosis if the clipped area remains patent. Parrish and co-workers have shown that large collaterals develop early after ligation of the inferior vena cava and these allow passage of moderate-sized clots. Thus we feel that clipping provides a clear advantage in limiting the size of collateral and postoperative emboli. Operative death and morbidity are largely related to pre-existing disease. Deaths are seen mainly in patients with large pulmonary emboli and postoperative leg edema is seen usually in patients with pre-existing thrombosis of iliofemoral veins. Heparin anticoagulation should be continued from the immediate postoperative period unless there is a specific contraindication.

The clinical syndrome of recurrent small emboli with development of cor pulmonale is best treated by medical means, since small emboli would likely continue through collateral channels following clipping or ligation of the inferior vena cava.

When occlusion of more than 70 per cent of major or equivalent vessels is demonstrated by angiography and the patient remains in shock refractory to vasopressors and other supportive measures, surgical removal of the clot is in order. Angiographic confirmation of massive embolism is essential, as thoracotomy usually results in death if the diagnosis is incorrect. The operative mortality rate of correctly diagnosed massive embolism is in the range of 40 per cent, further emphasizing the need for careful patient selection. Preliminary femoral vein to femoral artery bypass may be very helpful in allowing the patient to tolerate the thoracotomy. Interruption of the inferior vena cava should be performed immediately following the embolectomy and anticoagulation started 24 hours later.

Septic embolism. The diagnosis of septic embolism can be suspected by pulmonary infiltrate in the presence of septic thrombophlebitis, especially of pelvic veins. Current recommended treatment of septic embolism is ligation of the inferior vena cava and ovarian veins. Heparin therapy may be contraindicated because of potential bacterial invasion of lung arterial walls which may cause massive lung hemorrhage in the presence of anticoagulation.

Fibrin emboli (defibrination syndrome). The diagnosis of fibrin emboli should be suspected when shock or low cardiac output is found in the presence of disease known to produce hypercoagulability, such as abruptio placentae with leak of amniotic fluid into systemic veins, following prolonged circulatory bypass, or in the presence of gram negative infection. The diagnosis may be confirmed by laboratory assay of clotting factors.

Since the etiology of fibrin emboli is intravascular hypercoagulability, the treatment of choice is clearly heparin in adequate dose. Since pulmonary edema is frequently associated with these syndromes and is suspected to result from perivascular inflammation, corticosteroid therapy is probably also in order. A frequently employed steroid is prednisolone in a dose range of 60 mg. per 24 hours given intramuscularly. Anticoagulant and steroid ther

apy should probably be continued for at least 72 hours after the disease process which causes intravascular hypercoagulability has been controlled.

Fat emboli. Globules of neutral fat 10 to 40 μ in diameter enter systemic veins when veins serving fat depots are ruptured. These globules, which are small enough to pass through arteries and even arterioles, impact in and obstruct pulmonary capillaries. As capillaries are obstructed by fat, they are no longer available for oxygen transfer and hypoxia may develop as a result of impaired alveolocapillary oxygen diffusion. When sufficient numbers of capillaries have been obstructed by fat, increased vascular resistance is reflected by a rise in pulmonary arterial pressure, and the precapillary arteriovenous shunts open, allowing the venous blood which carries fat droplets access to the systemic circulation. The systemic manifestations of fat emboli (cerebritis, etc.) probably result from direct passage of neutral fat through pulmonary arteriovenous anastomoses opened in response to pulmonary hypertension. The chest x-ray appearance of fine reticular infiltrate probably results from perivascular edema and inflammation. The characteristic lag time of 24 to 96 hours in development of the syndrome implies that the entry of fat into the systemic veins continues over a prolonged period of time, rather than occurring as an acute massive leak.

The diagnosis of fat embolism should be suspected whenever diffuse infiltrates appear in the chest x-ray following major trauma to fat depots, especially to long bones. In nonfatal cases, the diagnosis frequently cannot be confirmed, since demonstration of fat in the urine requires that venous blood bypass pulmonary capillaries.

TREATMENT. Lung parenchyma is rich in lipase, and hence, if the continuing fat leak is stopped, neutral fat impacted in capillaries is metabolized to soluble fatty acids, and capillary blood flow is re-established. Treatment, therefore, should be generally supportive and aimed at preventing continued leak of fat into systemic veins. To this end, strict immobilization of the injured limbs is essential. Heparin therapy is frequently advocated because of its known effect in clearing chylomicra from the circulation. There is no evidence, however, that heparin has any effect on neutral fat droplets in the size range of 10 to 40 μ. In fact, heparin may be contraindicated as it prevents formation of clot in the ruptured veins of the injured fat depot, and therefore, may perpetuate the leak of neutral fat into systemic veins. Alcohol has been advocated to block lipase activity on the theory that the pulmonary inflammation results from local release of fatty acids. This view is not supported by chemical analyses of lung tissue for fatty acid content following fatal fat embolism. Since alcohol impairs lipase activity essential for the clearing of fat from lung capillaries, it may be contraindicated. Steroids may be helpful in reducing undesirable effects of perivascular inflammation on lung function. Oxygen and continued assisted ventilation should be used when necessary to correct hypoxia.

REFERENCES

1. Springate, C. S., Fechner, R. E., Scott, R. C., Jystad, G. R., and O'Neil, R. M.: Disappearance of clot emboli in rabbits, Arch. Path. 73:407, 1962.
2. Fred, H. L., Axelrad, M. A., Lewis, J. M., and Alexander, J. K.: Rapid resolution of pulmonary thromboemboli in man, J. A. M. A. 196:1137, 1966.
3. Thomas, D. P.: Treatment of pulmonary embolic disease, New England J. Med. 273:885, 1965.
4. Vigran, I. M.: Clinical anticoagulant therapy, Philadelphia, 1965, Lea & Febiger, Publishers.
5. Miles, R. M., Chappell, F., and Renner, O.: A partially occluding vena cava clip for prevention of pulmonary embolism, Am. Surg. 30:40, 1964.
6. Taber, R. E., Zikria, E., Hershey, E., and Conrad, L.: Prevention of pulmonary emboli with vena cava clip, J. A. M. A. 195:889, 1966.
7. Parrish, E. H., Adams, J. T., Bries, W. J., Burget, D. E., and DeWeese, J. A.: Pulmonary emboli following vena caval ligation, Arch. Surg. 97:899, 1968.
8. Love, J., and Stryker, W. S.: Fat embolism: A problem of increasing importance to the orthopedist and the internist, Ann. Int. Med. 46:342, 1957.

Annotations

Anticoagulants in renal disease

Thrombosis of the small blood vessels in the kidney is a prominent feature in some renal lesions such as thrombotic thrombocytopenic purpura, microscopic polyarteritis and allograft rejection. Thrombosis may play a part in a much wider range of renal disease such as lupus nephritis, scleroderma, and malignant hypertension (Kincaid-Smith[14]), and Vassalli and McCluskey[9] have drawn attention to the importance of thrombosis in glomerular capillaries in glomerulonephritis.

The renal blood flow which represents 20 per cent of the cardiac output would be considerably reduced by multiple small vessel thrombi in the kidney and this would be reflected in corresponding diminution in renal function. It therefore seemed appropriate to investigate the effects of anticoagulants in renal disease, particularly in patients with acute renal failure which is usually fatal when due to diffuse vascular or glomerular lesions (Kincaid-Smith[9]). Our own experience[11] in such cases is similar to that in other reported series (Merrill,[14] Pernoff,[15] Berlyne and Baker[4] and Alwall, Brun, Hatt, Harrison, Forland, Lee,[13] and their associates). Very few patients with acute renal failure due to diffuse vascular or glomerular lesions show any recovery of function and the few that do usually have persisting severely impaired renal function.

In selecting the type of anticoagulant treatment for patients with acute renal failure we decided to use continuous intravenous heparin in high doses sufficient to keep the coagulation time between 25 and 40 minutes.[11] The evidence from experimental nephritis showed that both heparin and coumarin anticoagulants had a striking effect on the pathogenesis reducing the severity of lesions and preventing crescent formation and progressive glomerular sclerosis (Silfverskiold, Kleinerman[12] and Vassalli and McCluskey[13]). Vassalli and McCluskey[13] suggested that it may be necessary to achieve an anticoagulant effect very close to the level at which hemorrhage occurs and we thought that we could achieve this more safely in man with heparin than with the coumarin group of drugs. Heparin infusion was continued for 2 to 6 weeks and followed by phenindione combined with dipyridamole. The latter drug was used because it is said to reduce platelet adhesiveness and thrombus formation and is free of side effects (Emmons and associates). Recent evidence suggests that the combination of a coumarin type of drug with a drug which inhibits platelet aggregation and thrombus formation is likely to prove more effective in the treatment of thrombotic diseases in man than coumarin drugs alone (Sullivan and associates[17]).

We treated six consecutive patients who presented to this unit with oliguric acute renal failure due to diffuse glomerular or vascular disease. Histologic confirmation of the diagnosis was obtained in all patients. Three had diffuse proliferative glomerulonephritis, two had polyarteritis nodosa, and one had thrombotic thrombocytopenic purpura. All six patients showed recovery of renal function to normal or near normal levels and in five patients rapid increase in urine output and improvement in renal function followed infusion of heparin. These patients had failed to respond to adequate hydration, mannitol, or to large doses of furosemide. In three patients renal function deteriorated when heparin was stopped, and this together with the rapid improvement which followed heparin administration suggests that heparin had some direct beneficial effect on the underlying renal disease. Two patients died from diffuse vascular lesions in other organs but four are well 5 to 12 months after the onset of renal failure and have blood urea levels between 23 and 40 mg per 100 ml. Our experience suggests that early treatment is important. Some of our patients were treated within hours of admission to hospital.

All patients also received other treatment with steroids or immunosuppressive drugs, and it cannot therefore be claimed that the improvement was due to heparin alone. However, in view of our previous disappointing results with these drugs, and as there was no apparent improvement at the time at which they were started, it seems likely that heparin played a major role in improving renal function.

All the patients had diseases which are presumed to have an immunologic basis, and fluorescent antibody techniques suggest that the primary damage is immunologic in such cases. Formation of fibrin thrombi on the damaged endothelial cells, although a secondary factor, may well be an important cause of impairment of function in glomerulonephritis and in diseases of the small blood vessels in the kidney. Its importance in this respect has been demonstrated in allograft rejection and in experimental glomerulonephritis.

It is difficult to understand the mechanism underlying the prompt increase in urine output within hours of heparin administration unless thrombosis and fibrinolysis are progressing rapidly and simultaneously in these damaged glomeruli and vessels. This has been postulated in experimental nephritis and could explain rapid improvement in renal function if heparin prevented new thrombus formation in vessels cleared by natural fibrinolytic processes. If this is the explanation, one might have expected a more dramatic result from streptokinase than

observed in the one patient on whom it was tried on [illegible] occasions. Heparin has many actions: It is said to enhance fibrinolysis, neutralize complement, and modify many allergic phenomena (Engelberg[5]), and these could have contributed to its effect in our patients.

No effective treatment for glomerulonephritis is yet available and this common disorder contributes most patients to dialysis or transplantation programmes. Our experience with anticoagulants together with experimental evidence that the severity of histologic lesions can be considerably reduced by anticoagulants suggests that more extensive trials should be conducted in glomerulonephritis.

Our experience in acute renal failure makes us reluctant to conduct controlled trial in such patients, however we are conducting controlled trials in other less acute forms of glomerulonephritis.

Perhaps the most important and exciting aspect of anticoagulants in the treatment of renal disease lies in the prevention not only of renal failure but in the prevention of vascular and glomerular lesions.

The vascular and glomerular lesions which develop in days or weeks in the rejecting allograft are almost identical with those seen in certain other renal diseases.[10] Observed changes in graft rejection and experimental nephritis suggest that thromboses within glomerular capillaries in lesions, such as thrombotic thrombocytopenic purpura, lupus nephritis, and other forms of glomerulonephritis, are important in producing progressive glomerulosclerosis. If this is so it may be possible to prevent this with effective anticoagulant treatment. Even more controversial is the possible effect of anticoagulants on vascular lesions in the kidney. In allografts, anticoagulants seem to modify the vascular lesions perhaps preventing the progressive intimal fibrosis which leads to renal failure following renal transplantation (Kincaid-Smith, unpublished observations). If the pathogenesis of the vascular lesions of malignant hypertension, scleroderma, polyarteritis nodosa, and thrombotic thrombocytopenic purpura is similar to that observed in allograft rejection, namely organization of mural thrombi resulting in progressive intimal thickening, then it may be possible to prevent the development of progressive vascular lesions in these conditions using anticoagulants combined with conventional methods of treatment in these disorders.

There should be interesting developments in this field over the next ten years and perhaps the cardiologist and nephrologist will draw closer together again because of common interest in the prevention of progressive vascular sclerosis—the major cause of death in both fields.

Priscilla Kincaid-Smith,
B.Sc (Witwatersrand), M.D (Melb.),
F.R.C.P F.R.A.C.P D.C.P
First Assistant in Medicine
University of Melbourne
Physician-in-charge Medical Renal Unit
Royal Melbourne Hospital
Victoria 3050 Australia

REFERENCES

1. Arvall N., Erlanson, P., Tornberg, A., Falck, C. M., and Moell, H.: Two cases of glomerular nephritis with severe oliguria for 75 days. Clinical course, roentgenological studies on kidney size, and post-mortem findings, Acta med. scandinav. 161:85, 1958.
2. Berlyne, G. M., and Baker, S. B. De C.: Acute anuric glomerulonephritis, Quart. J. Med. 33:105, 1964.
3. Brun, C., Gormsen, H., Hilden, T., Iversen, P., and Raaschou, F.: Kidney biopsy in acute glomerulonephritis, Acta med. scandinav. 160:155, 1958.
4. Emmons, P. R., Harrison, M. J. G., Honour, A. J., and Mitchell, J. R. A.: Effect of dipyridamole on human platelet behaviour, Lancet 2:603, 1965.
5. Engelberg, H.: Heparin metabolism, physiology and clinical application, Springfield, Ill., 1963, Charles C Thomas, Publisher.
6. Forland, M., Jones, R. E., Easterling, R. E., and Forrester, R. H.: Clinical and renal biopsy observations in oliguric glomerulonephritis, J. Chron. Dis. 19:163, 1966.
7. Harrison, C. V., Loughridge, L. W., and Milne, M. D.: Acute oliguric renal failure in acute glomerulonephritis and polyarteritis nodosa, Quart. J. Med. 33:39, 1964.
8. Hutt, M. S. R., Pinniger, J. L., and de Wardener, H. E.: The relationship between the clinical and the histological features of acute glomerular nephritis, Quart. J. Med. 27:265, 1958.
9. Kincaid-Smith, P.: The clinical value of renal biopsy. I. Internat. Congr. Nephrol. 2:178, 1966.
10. Kincaid-Smith, P.: Histological diagnosis of rejection of renal homografts in man, A, Lancet 2:849, 1967.
11. Kincaid-Smith, P., Saker, B. M., and Fairley, K. F.: Anticoagulants in irreversible acute renal failure, Lancet 2:1360, 1968.
12. Kleinerman, J.: Effects of heparin on experimental nephritis in rabbits, Lab. Invest. 3:495, 1954.
13. Lee, H. A., Stirling, G., and Sharpstone, P.: Acute glomerulonephritis in middle-aged and elderly patients, Brit. Med. J. 2:1361, 1966.
14. Merrill, J. P.: The use of the artificial kidney in the treatment of glomerulonephritis, J. Chron. Dis. 5:138, 1957.
15. Persoff, D.: Recovery from prolonged oliguria in acute glomerulonephritis, Lancet 1:1347, 1965.
16. Silverskiold, B. P.: Heparin und experimentelle glomerulonephritis, Skan. Arch. Physiol. 83:175, 1940.
17. Sullivan, J. M., Harken, D. E., and Gorlin, R.: Pharmacologic control of thromboembolic complications of cardiac-valve replacement. A preliminary report, New England J. Med. 279:576, 1968.
18. Vassalli, P., and McCluskey, R. T.: The pathogenic role of the coagulation process in rabbit Masugi nephritis, Am. J. Path. 45:653, 1964.
19. Vassalli, P., and McCluskey, R. T.: The coagulation process and gl[illegible] [illegible] Med. 39:179, 1965.

Differences in the heart as a generator of the QRS and ST-T deflections*

The purpose of this communication is to call attention to the different cardiac location of events responsible for the QRS and the ST-T deflections of the electrocardiogram (ECG) and to suggest that some features of these deflections may be the result of their different site of origin.

At a given moment during ventricular activation, boundaries of potential difference exist at a limited number of locations within the heart. Activation of an individual cell occurs in a few milliseconds during the rising phase of the transmembrane action potential, and total activation of the normal human ventricles is completed in about [illegible] msec. The process can be described as a moving

*The above work was supported in part by Research Grant 11 1011J and Training Grant 11-1043C from the National Heart Institute, United States Public Health Service.

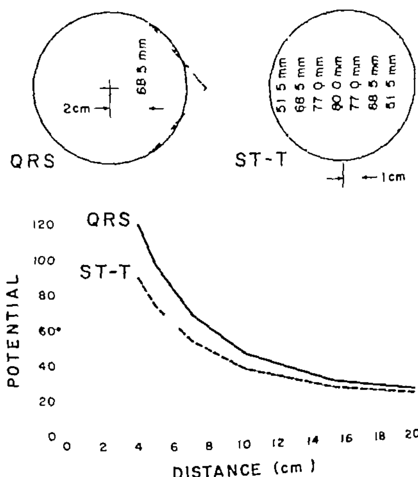


Fig. 1. The circles represent the ventricular mass. *QRS* represents activation, with a single boundary of potential difference between resting and depolarized cells. A single electrode site is shown, with the angle formed by the electrode site and the ends of the boundary. This angle represents the potential measured by the electrode. *ST-T* represents repolarization, with *7* equally spaced parallel boundaries of potential difference representing the distributed nature of recovery. The graph depicts the potential (subtended angle) measured at all electrode sites 4 to 20 cm distant from the centers of the circles. Potentials measured from the localized source are labeled *QRS* on the graph and averaged potentials from the distributed source are labeled *ST-T*. The two curves do not coincide, indicating that a distributed potential source produces a different potential than a localized source, especially at the electrode locations near the source.

boundary between activ and resting muscle and at any instant the boundary has a particular locus within the heart

I contrast, boundaries of potential difference are distributed throughout the ventricular mass during most of the recovery process I each cell, recovery begins immediately following activation and is complete only after several hundred milliseconds. During recovery boundaries of potential difference exist between cell or groups of cells in which recovery has reached different tages and action potential downstrokes are t different levels Recovery is thus occurring in successivel larger portions of the entricular mass activation proceeds. After activation is complet recovery in various stages of completion exists in ll part of the ventricles. The ST T deflection arises from this changing pattern of idely distributed potential differences. These considerations suggest that some of the differences in electrocardiographic manifestations of excitation and recovery may be the result of localized origin of the former nd distributed origin of the latter This factor has not been specifically considered previously in relation to ECG form.

T evaluate the effect of the differing sites of QRS and ST T origin, the graphic analysis ill trated in Fig 1 was carried out. The entricular mass was epresented by a circle 8 cm. in diameter Six electrode sites t distances of 4 t 20 cm. from the center of the circle were considered. These dimensions ere chosen to pproximate those in volved in human electrocardiography Excitation as represented by single boundary 2 cm. from the center of the circle, as illustrated in the portion of Fig. 1 labeled QRS Repolarization as represented by seven parallel boundaries equally spaced across the same circular entricular mass as show in the portion of the figure labeled ST T Potential at each electrode site was taken as the angle formed by lines connecting the boundary ends th the electrode site Potential was plotted as function of electrode distance from the center of the entricle. I the case of the distributed potential source (ST T), all potentials for a given lectrode sit ere averaged before plotting

It is evident f om the graph that the t curves do not coincide The effect of electrode distanc on potential from localized source differ f om that due to distributed one and the difference is great est when electrode sites are closest to the heart Electrode sites nearest the distributed source are still relatively distant from some portions of that source. Thus, for the nearer electrode sites the boundaries nearest the electrode ontribute disproportionately larger share to the average potential than boundaries further from the elec ode As the electrode d tance from the heart is increased the exaggerated contribution of the nearer boundaries diml ishes so that electrode sites further f om the heart are relativel less affected by whether the source is localized or distributed This general behavior is predictable but the graph on Fig 1 illustrates the order of magn tude of effect t be expected w th the tw sources using realistic cardiac dimen sions nd elect ode distances.

It ppears f om these onsiderations that the ole of the localized origin of QRS nd distributed origin of the ST T deflection should be examined in linical nd experimen l tudies specifically designed for th purpose For example t seems likely that variations in heart position will ha different effect on QRS nd ST T deflections It lso seem likely that the different sit of QRS nd ST T origin may be factor in bod surface isopotential distribution Taccardi[3] has noted different behavior of excitation and recovery in uch maps with the QRS showing periods of nondipolarit nd the normal h man ST T beha ng in niforml d polar manner It also ppear hat localized lesions hich increase the con ribution of certai cardiac areas to the ST T deflection, may cause that deflection to beha more nearl like the QRS complex Further t may be desirable t take account of the localized origin of QRS nd distributed source of the ST T deflection in lead stem design In any event, t is orth hile that the degree t hich different rdiac sites of origin of the QRS and ST T influence he form of these deflections be determined ontribution t nderst nding the physiologic basis of he ECG

C Thomas F uchs M D
Department of Medic ne
State U versity of New York
Upstate Medical Center
Syracuse N Y
Gerhard Baal Ph.D
Electrical Engineering Department
Syracuse U versity
Syrac se N Y
M rv J B rgess M.D
K y Mills M D
J A Abildskov M D
U ity of Utah College of Medicine
Salt Lake Cit Utah

REFERENCES

1 Harumi K Burgess M J and Abildskov J A A theoretic model of the T w ve, Circulat on 34:657 1966
2 Burgess, M J Harumi, K., and Abildskov J A Application of a theoretic T-wave model experimentally induced T ve bnormalities Circulation 34:669 1966
3 Taccardi B Body surface distribution of equipo ential lines during tral depolarization and ricular repolarization, Circulation Res. 19:865 1966

Peripheral chemoreceptor regulation of heart rate

The precise nature of cardiac acceleration with exercise is not yet f lly understood. Neurogenic mechanisms, such as release of vagal cardio-in-h bitory tone and increased activity of the sympathetic cardiac nerves, are predominant. Central control is dependent upon (1) afferent impulses f om receptors originating in the working muscles nd joints and acting in proportion to the rate of work (2) facilitating cardiac nervous influences f om cortical centers and possible irradiation from the motor tracks (3) cardio-accelerator reflexes from the chemoreceptors of the carotid nd aortic bodies (4) depressor reflexes from the pressure receptors in the carotid sinus and aortic arch.

Recently new theory of cardiac acceleration during exercise was presented by Stegeman. The theory postulates peripheral chemoreceptors located within the interstitial spaces between muscle fibers and capillaries, sensitive to CO_2 and H concentration. Evidence for this theory is derived from experiments in humans in which a rise in heart rate was obtained during local arrest of the circulation with tourniquets applied t the limbs. The increase in heart rate was shown to be proportional t the mag itude of the oxygen debt incurred during arrest of the circulation. Further evidence was derived from experiments with afferent nerve stimulation, analogue-models d exercise tests.

Stegema theory is ttractive since it may explain some unsolved problems of circulatory adjustments d ring high intensity work with small muscle groups and isometric work. It is generally accepted that there is linear relationship between heart rate and oxygen consumption during exercise. The relationship is quite different during exercise which engages only a small number of muscles. In this situation there is a proportionally higher heart rate in relation to oxygen consumption.

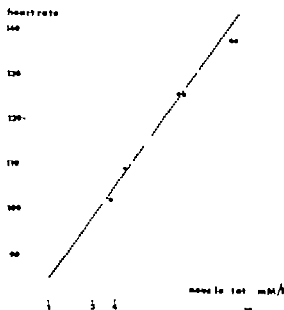


Fig 1 Plot of venous lactate versus heart rate d ing graded muscular exercise.

Exercise with restricted arterial supply t the working muscles is situation which leads early to anaerobic conditions and the production of acid metabolites within the muscles (as reflected by the high degree of lactic acid production). This condition therefore represents an ideal situation to test the above hypothesis. A high level of lactic acid should create state which activates the peripheral chemoreceptors with a parallel ugmentation of heart rate. Recently Zetterquist and collaborators[3] in metabolic studies of the peripheral circulation in patients with segmental arterial occlusions in the lower extremities presented data on the femoral venous lactate concentration and heart rate d ring exercise Fig 1 represents plot of venous lactate versus heart rate during graded muscular exercise. The diagram illustrates a clearcut correlation between these two parameters—a proportional rise of heart rate with increasing lactate concentration. This apparent correlation which corresponds to the actual situation in patients seems to support Stegeman s hypothesis. The quantitative importance of peripheral chemoreceptor influences on heart rate should be investigated further but it seems reasonable to assume that such mechanism may act as an additional reinforcing stimulus to increasing heart rates during exercise even under physiological conditions.

The peripheral "chemoreceptor theory of Stegeman is an ttractive hypothesis for the possible explanation of other situations with unproportional elevation of heart rate during exercise, e.g. manifested in patients with vasoregulatory asthenia. A striking feature in these patients is the impairment of the tissue-oxygen extraction. This is connected also by supernormal elevation of lactic acid during exercise, an indication of early anaerobic metabolism due t abnormal distribution of blood flow during exercise with a decreased proportion of blood flowing through the exercising muscles. In these cases beta-blocking agents have been reported to counteract excessi tachycardia at rest and during exercise. This action has hitherto solely been attributed t the negative chronotropic cardiac action of the drug However a peripheral action of beta-blockers on carbohydrate metabolism has been reported, and therefore it seems reasonable to assume that the blockers also influence glycolysis. Such peripheral metabolic effect of beta-blockers may reduce heart rate by itself by lowering lactic acid release. F rther research along these lines may be fruitf l.

Olav Thulesius M.D.
Head Department of Clinical Physiology
Central Hospital
Växjö Sweden

REFERENCES

1. Robinson, S. Physiology of muscular exercise, in Mountcastle, V. B., editor: Medical physiology vol. I, St. Louis, 1968, The C. V. Mosby Company p. 544.
2. Stegeman, J. Zum Mechanismus der Pulsfrequenzeinstellung durch den Stoff echsel, I IV Pflügers Arch. Ges. Physiol. 276:481 1963.
3. Pernow B., and Zetterquist, S. Metabolic evaluation of the leg blood flow in claudicating patients with arterial obstructions at different levels, Scandinav J Clin. Lab. I vest. 21:277 1968.
4. Bellman, S and Zetterquist, S: Oxygen tili-zation and lactate formation in the leg during exercise before and after arterial reconstruction patient with intermitt t claudication, Acta chir scandinav 133:43 1966.
5. Lofström, B., and Zetterquist, S. The effect of lumbar sympathetic block upon nutritive blood flow capacity in intermittent claudication Acta med. scandinav 182:23, 1967
6. Carlsson, L. A., Pernow B and Zetterquist, S. Studies on the peripheral circulation and metabolism in man, Acta med. scandinav 172:389 1962.
7. Fitzgerald, J D The value of propranolol in disturbances of a tonomic control of the car diovascular system, Internat. J Clin. Phar macol. 1:298 1968.
8. Kotler M. N Berman, L., and Rubenstein, A. H.: Hypoglycemia precipitated by propranolol Lancet 2 1389 1966.

Potassium-glucose-insulin

Death from myocardial infarction is the biggest hazard to adult lif in the relatively affluent countries. The principal mechanism of death is termination of effective myocardial contraction by entricular fibrillation or asystole. It is natural, therefore, that much investigative effort is concentrated on the prevention or immediate correction of such lethal factors.

Although much remains to be discovered about the mechanism of muscular contraction, whether it be myocardial or any other sort, good deal is known about the electrolyte changes associated with muscle contraction and the defects that occur in injured muscle.

It is reasonably certain that the initiation of ventricular fibrillation in myocardial infarction is similar to the effects of an electric current and can be regarded as due to electrolyte disturbances. While total cell destruction occurs in the center of a zone of myocardial infarction, the cells t the periphery while relatively anoxic, are capable of surviving The anoxic state is characterized by movement of potassium out of and sodium into the cell. Papers by Sodi-Pallares and associates have suggested treatment t replace the potassium lost from the damaged cells and hence reduce arrhythmias. This can be regarded as polarizing procedure to correct the ionic depolarizing of anoxia. The clinical trials of these workers yielded encouraging results, but the number of patients studied was not large and the controls were not rigorous. They[1] conclude paper on this subject with this paragraph "W are cognizant that only in the f ture after great deal of evidence has accumulated will w know the full value of the polarizing treatment. However w feel that it will emerge as one of the most important forms of treatment in the field of cardiology and is likely to find application in fields outside of cardiology

Mittra, in controlled sequential clinical trial, tested polarizing treatment, which consisted of an oral potassium supplement with injected sol ble insulin and oral glucose, in 170 patients with acute myocardial infarction. Up to the fourteenth day the mortality rate in the treated patients was only 11 7 per cent as compared with 28.2 per cent i the control group It appeared that the principal effect of the potassium, glucose and insulin (P G.I) as reducing the umber of deaths ttributable t arrhythmias This lowered mortality rate was also found by Mittra[3] in series of 200 patients all treated with P G I nd compared with the rate recorded in the same hospital over the previous 13 years.

The British Medical Research Council Working Party on the Treatment of Myocardial Infarction decided to test this treatment in large-scale trial involving 13 medical centers. This test made use of group of clinicians and hospitals who had worked together for some 13 years on experiments testing anticoagulant therapy in myocardial infarction. The trial was carried out between April 1 1967 and March 31 1968. All patients considered to have had myocardial infarction within the previous 48 hours, without restriction of age or sex, who were not diabetic, on insulin or hypoglycemic drugs, and who had no strong clinical evidence of uremia were admitted to the trial. Allocation t the P G I trials was indicated by sealed envelopes which contained randomly selected number The results were studied on the basis of death or survival for 28 day

Admitted to the trial were 966 patients, 13 were excluded from analysis because the episode of infarction had not occurred within the previous 48 hours and a further 5 were excluded because they discharged themselves shortly after admission against medical advice. I 128 of the remaining 986 patients the initial diagnosis of myocardial inadequately supported. The ys in the treated group was 0 patients) and in the (109 of 430 patie

dea
j

clearly no significant difference in the incidence of cardiac arrhythmias. This decisive result completely failed to associate P.G.I. trials with any benefit.

Pentecost and associates in a clinical trial of 200 patients with acute myocardial infarction treated with a wholely intravenous P.G.I. procedure, likewise found no evidence of any benefit.

Consideration was given to the negative Medical Research Council result in comparison with the positive result obtained by Mittra. The laws of chance dictate that apparently significant results sometimes arise in the absence of any true difference. In Mittra's trial, a reduction in mortality rate represents a difference between 10 and 24 deaths which because of the sequential design of the trial was significant only at the 5 per cent level. The data from the larger Medical Research Council trial show that substantial differences in mortality rate between treatment groups occurred in opposite directions at two of the centers. The data from one of those centers would have supported Mittra's findings, while the data from the other center would have accorded a harmful effect of comparable magnitude to the P.G.I. treatment.

A statistical lesson to be learned is that a 5 per cent significance level is not really adequate, and that there is safety in numbers. This negative result is disappointing because such a simple, safe, and effective therapy would have been a great blessing.

H. Mehdi [illegible], F.R.C.P., F.A.C.P.
Queen Elizabeth Hospital
Edgbaston
Birmingham, England

REFERENCES

1. Sodi-Pallares, D., Bisteni, A., Medrano, G. A., de Micheli, A., Ponce de Leon, J., Calva, E., Fishleder, B. L., Testelli, M. R., and Miller, B. L.: The polarizing treatment in cardiovascular conditions, electrolytes and cardiovascular diseases, vol. 2, New York, 1966, S. Karger, p. 198.
2. Sodi-Pallares, D., Testelli, M. R., Fishleder, B. L., Bisteni, A., Medrano, G. A., Friedland, C., and de Micheli, A.: Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction, Am. J. Cardiol. 9:166, 1962.
3. Mittra, B.: Potassium, glucose and insulin in treatment of myocardial infarction, Lancet 2:607, 1965.
4. Mittra, B.: Potassium, glucose and insulin in treatment of heart block after myocardial infarction, Lancet 2:1438, 1966.
5. Mittra, B.: Potassium, glucose and insulin in treatment of myocardial infarction, Brit. Heart J. 29:616, 1967.
6. Medical Research Council Working Party: Report on the Treatment of Myocardial Infarction: Potassium, glucose and insulin treatment for acute myocardial infarction, Lancet 2:1355, 1968.
7. Pentecost, B. L., Mayne, N. M. C., and Lamb, P.: Controlled trial of intravenous glucose, potassium, and insulin in acute myocardial infarction, Lancet 1:946, 1968.

Book reviews

CIRCULATION IN SKELETAL MUSCLE. Proceedings of an International Symposium held at Smolenice, Czechoslovakia, edited by O Hudlická, Oxford, 1968, Pergamon Press, Inc., 356 pages. Price $15.00.

These are the proceedings of symposium held in Czechoslovakia in 1966 The contributors are leading investigators in the field. The subjects discussed are broad. Among the aspects presented are central nervous regulations of skeletal muscle function, effect of angiotensin on visceral and muscle circulation, effect of adrenergic blockade on forearm blood flow blood flow nd skeletal muscle metabolism, autoregulation of skeletal muscle flow muscle circulation ischemia, along with many others. The publication is organized like the well known and excelle t ones of the Ciba Symposia. The discussions are most interesting This is very good book hich should interest all students of circulation.

DISEASES OF THE HEART AND CIRCULATION Ed. 3 by Dr Paul Wood, revised by his friends and colleagues, Philadelphia, 1968, J B. Lippincott Company 1,164 pages Price $29.00.

This is an outstanding book which first appeared about 20 years ago Unfortunately Paul Wood' untimely death interfered with the publication of third edition. Fortunately however leading cardiologists of Britain have joined Dr Walter Sommerville to produce this third edition. These editors and contributors have continued the same format of the previous editions to bring the book up to date. The book is expanded considerably even though the style remains the same This is an excellent book, one of the best in cardiology Sommerville and his associates ha rendered fine service to medicine in perpetuating Wood book.

CLINICAL ASPECTS OF OPERABLE HEART DISEASE By Donald R Kahn, M D Ruth H Strang, M D and William S Wilson, M D New York, 1968, Appleton-Century-Crofts, Inc Division of Meredith Pub Co 363 pages Price $16 00

The authors have written book which should not only interest cardiac surgeons, but cardiologists as ell. The book consists of 24 rather short chapters hich include the congenital and acquired types of heart disease for which surgery performed The chapters are well-organized and nicely illustrated The pathophysiologic nd clinical features of the various diseases and congenital defects are discussed f om the cardiologic and surgical point of view There is short chapter on transplantation. The book is useful one ritten by surgeon, pediatrician, and cardiologist. Those ho are involved actively in such problems will find the book of relatively little interest whereas beginners may like such a book which is concise nd includes the prevailing opinions at the present time.

BEAT TO BEAT HEMODYNAMIC EFFECTS OF LU G IN FLATION AND NORMAL RESPIRATION IN ANALSTHE TIZED AND CONSCIOUS DOGS. By Andre A. Charlier Bruxelles, 1968, Editions Arscia S. A 112 pages.

This relatively brief monograph summarizes the experiments of Doctor Charlier in which he recorded the time-courses of pressure and volume blood flow in the pulmonary system of dogs. His methods were conventional ones. Measurement were made with the chest open and with it closed. H describes his method and result very clearly and presents his data in detail. The influence of the variations of respiration re shown. The studies are important and should be of special interest to those studying pulmonary circulation, segment of the cardiovascular ystem long neglected This is an important contribution to understanding of pulmonary circulation.

DAS EKG NACH OPERATIONEN AM HERZEN UND AN DEN GROSSEN GEFÄSSEN By Ernst Kriehuber Stuttgart, 1968, Georg Thieme Verlag 256 pages

This is nice presentation of changes in the electrocardiogram produced by surgery for various types of cardiac disease The pre- nd postoperative electrocardiograms are clearly defined and nicely illustrated An electrocardiogram of transplanted heart is included for curiosity The authors included surgical repair of congenital defect and various types of acquired cardiac disease including valvular defects and valve replacements The duration of follow-up after surgery varied, of course This book is the first one devoted entirely to such an aspect of cardiology It contains interesting material clearly presented and caref lly documented.

BALLISTOCARDIOG APHY Edited by Dennis Deuchar Basel Switzerland, 1968, S. Karger AG 190 pages, Price $11 10

This book contains the proceedings of the Sixth European Congress on Ballistocardiography held London, Apr 3-4 1967 The proceedings consist of series of papers concerning arious physiologic, pharmacologic, and clinical aspect of BCG. These papers should interest those who are working with BCG The papers are almost entirely from European workers and, therefore, reflect the ideas from that part of the world. These papers further support the need for much more clinical investigation before BCG can become an established procedure in the prac of medicine, as has electrocardiography

GRUNDLAGEN DER DYNAMIK DES ARTERIENPULSES. By E. Wetterer and Th. Kenner Berlin 1968 Springer Verlag 379 pages. Price $24.00

This is an excellent monograph of studies of and hemodynamic principles of arterial pulsations and blood flow Experimental data as well as theoretic considerations are well selected and clearly discussed. The older and the more recent literature are reviewed, including the ork of Otto Frank, Philipp Broemser and others. The uthors support their discussions with mathematic analyses and well-selected illustrations. The bibliography is good and should be useful to readers who are interested in greater detail and the original studies This is good book.

√Books received

ADVANCES IN INTERNAL MEDICINE. VOL. XIV 1968. Edited by I Snapper and Gene H. Stollerman, Chicago, 1968, Year Book Medical Publishers, Inc. 367 pages. Price $12.00

AUSCULTATION OF THE HEART ed. 3 By Richard W D Turner Baltimore, 1968 E. & S. Livingstone, Ltd. and The Williams & Wilkins Company 53 pages. Price $4.00

BIOLOGICAL INTERFACES FLOWS AND EXCHANGES. By Francis P Chinard, M D Boston, 1968, Little Brown & Company 326 pages Price $7.50.

[illegible] ERCISE AND ALTITUDE MEDICINE AND SPORTS. 1 Edited by E. Jokl and P Jokl, Basel 1968, K[illegible]rger AG 199 pages. Price $13.90

I[illegible]CTION TO MEDICAL DECISION MAKING. By Lee B L[illegible]sted Springfield Ill. 1968 Charles C Th[illegible] P[illegible]blisher 271 pages. Price $18 75

LA GROSSE JAMBE. By R ymond Tournay Société Française de Phlébologie, Paris, 1968, L'Expansion Scientifique, 276 pages.

RECENT RESULTS IN CANCER RESEARCH VOL. 15. CARCINOID AND SEROTONIN By Boris Sokoloff, Edited by P Rentchnick, New York, 1968, Springer Verlag 121 pages. Price $6.00.

RHEOLOGY OF THE CIRCULATION By R L Whitmore, New York, 1968, Pergamon Press, Inc. 196 pages Price $9 00.

STORAGE OF BLOOD By B A. L H rn, London, 1968, Academic Press, Inc 167 pages. Price $7.50.

Author index*

*January pp. 1-132; February pp. 133-294 March, pp. 295-436 April, pp. 437-576 May pp. 577-718 June, pp. 719-856

Y

Z

Subject index*

A

*January pp. 1-132; February pp. 133-292; March, pp. 293-436; April, pp. 437-576; May pp. 577-718; June pp. 719-864.